PATHOGENESIS AND TREATMENT OF MIGRAINE

Fifty per cent of the population experiences a headache at least once a week. Migraine is the second most common cause of chronic daily headache with a lifetime prevalence of approximately 18% in women and 6% in men.[1]

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The most frequently encountered migraine syndromes include typical headache without aura and headache associated with focal neurological deficit, otherwise known as migraine aura.[2] Patients may experience both types during the natural history of their disease.[2] Migraine is best understood as a primary disorder of the brain. It is a form of neurovascular headache in which neural events result in dilatation of blood vessels that in turn results in pain.[3] Migraine attacks are episodic and vary within and among patients.

The pathogenesis of migraine is complicated and is best understood in the context of three key factors:[4]
- mechanism through which the attacks are triggered
- sequence of clinical events
- threshold for attacks.

The concept that migraine originates in the brain and can be triggered under various conditions argues in favour of a threshold that governs the incidence of attacks. Excitability of cell membranes in neurons in the occipital cortex appears fundamental to the brain's susceptibility to migraine.[5] Factors that increase or decrease excitability modulate the threshold for triggering attacks. Several abnormalities have been proposed to account for neuronal excitability in migraneurs. These include:[2]
- disturbances in magnesium metabolism
- calcium channel abnormalities, and
- mitochondrial defects.

A migraine attack is a response of the brain and its blood vessels to some trigger resulting in disordered neurogenic control of the intrinsic and extrinsic circulation.[2] External migraine triggers include stress, hormonal changes, changes in sleep patterns, alcohol and certain foods, trauma and exertion.[3,6]

In migraine with aura, visual disturbances are the most common, beginning with positive phenomena such as stars, complex geometrical patterns and fortification spectra followed by negative phenomena such as scotoma or hemianopia.[1] These symptoms are characteristically slow in both onset and progression.[2] Somatosensory symptoms, aphasia, hemiparesis and clumsiness occurring in a march-like progression are far less frequent. The pattern of symptoms indicates the spread of neurological dysfunction from the occipital cortex into contiguous regions of the parietal and temporal lobes. The aura usually subsides after approximately 30 minutes and is followed by one or more of the following symptoms:[1]
- headache
- nausea and/or vomiting
- photophobia and/or phonophobia.

The mean duration of an attack is 24 hours.

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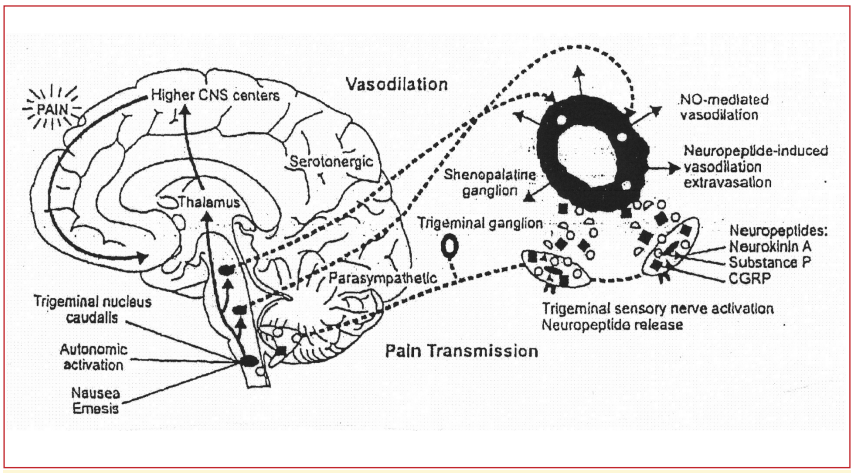

Fig. 1. Pathogenisis of migraine headache. Activation of the trigeminovascular system is pivotal to headache and its associated symptoms. Afferent fibres transmit nociceptive information to the trigeminal nucleus caudalis in the lower brain stem. Depolarisation of the trigeminol ganglion activates the trigeminovascular system, in which released neuropeptides (substance P, neurokinin A, CGRP) produce a neurogenic inflammatory response leading to vasodilation and extravasation.

Aura is characterised by a wave of oligaemia (low blood flow) that passes across the cortex at a rate of 2 - 6 mm/minute.[3] In 1994 Leao reported an experimental phenomenon of spreading depression (SD) in animal studies. Neuronal depolarisation is followed by suppression of neuronal activity in a wave that spreads across the surface of the brain. The migraine aura, exemplified by an expanding visual scotoma with preceding peripheral scintillation, is proposed as the clinical counterpart to SD.[2]

Investigation of Leao's model of SD in humans remains incomplete. Investigators have been limited to indirect measures of blood flow, but despite this have shown a decrease in cerebral blood flow in posterior regions of the cortex in some patients during an attack of migraine with aura. Focal hyperaemia, possibly related to neuronal depolarisation, precedes the spreading oligaemia.[2] Further studies using functional magnetic resonance imaging support the concept that migraine aura is due to neuronal dysfunction and not ischaemia. However, the headache phase has not revealed any consistent perfusion abnormality.[4] The question remains why some migraines are not preceded by focal neurological deficit despite decrease in cerebral blood flow in both subtypes. One explanation is that there may be a certain threshold to produce symptoms of aura.[2]

The mechanism by which the aura leads to headache remains to be definitively determined. Activation of the primary afferent neurons of the trigeminovascular system plays a pivotal role in the genesis of migraine.[4] Primary afferent fibres within the trigeminal nerve carry nociceptive information through the trigeminal ganglion and terminate in the nucleus caudalis, an area of pain processing in the brainstem. Depolarisation of trigeminovascular nociceptive neurons triggers the release of neuropeptides including substance P, calcitonin gene-related peptide (CGRP) and neurokinin A.[3] These neuropeptides are associated with a neurogenic inflammatory response, which leads to vasodilation, extravasation and activation of local cellular immune response. These events lower the threshold for reactivation, creating a positive feedback loop and resulting in perception of increasing pain.[3] The importance of central sensitisation relates to early treatment of the acute attack, as delays are likely to decrease medication efficacy due to the development of allodynia (non-painful stimuli are perceived as painful).[5] Fig. 1 illustrates the pathogenesis of migraine.

TREATMENT OF MIGRAINE

Treatment is classified into non-pharmacological and pharmacological therapy.

Non-pharmacological treatment

This includes education about the disorder and changes in lifestyle for avoidance of triggers. In patients with migraine, the brain does not tolerate the peaks and troughs of life well. The crucial message is to aim for regular habits rather than adhere to long lists of prohibitions. Thus regular sleep, regular meals, exercise, avoidance of dietary triggers and relaxation are all important in maintaining rhythmic life cycles.[6] Non-pharmacological treatment includes relaxation techniques, deep breathing, acupuncture and dietary modification.

The key in successfully managing migraine is to assess the impact of illness and to acknowledge migraine as a frequently debilitating and potentially enduring condition.[7] Subsequent steps include offering therapies based on frequency and severity of attacks, while addressing co-morbid and co-existent conditions. Suggestions that headache sufferers receive suboptimal care are validated by epidemiological studies, which report that migraine remains underdiagnosed and undertreated.[7]

Helping patients to acknowledge their condition by explaining the biology

behind the disorder will certainly lead to more effective control. Several instruments are available to assess the impact and severity.[7] These include:
- migraine disability assessment scale (MIDAS)
- headache impact test (HIT)
- migraine-specific quality of life instrument (MSQoL).

These scales provide a means for the patient and doctor to quantify levels of illness and evaluate how migraine affects work, social activities and family life. Successful treatment is possible if care is individualised according to patient needs. Related conditions and co-morbidities must be considered. Some medical disorders are more prevalent in migraneurs, such as:
- depression
- anxiety
- bipolar mood disorder
- Raynaud's phenomenon
- epilepsy
- stroke.

Pharmacological treatment

This is classified as 'acute' or 'prophylactic' treatment.

Treatment of the acute attack

The oldest known medical manuscript discovered in Egypt (approximately 1550 BC) mentions several cures for headache including anointing the head with ashes from the burnt skull of a catfish fried in oil. Over the centuries, treatment modalities have included potassium cyanide, strychnine, atropine, digitalis, hashish, hemlock and quicksilver compound. The first successful anti-migraine agent was used at the end of the 19th century. The progress of medical chemistry combined with mechanism-driven drug design led to the development of triptans.[5]

The pharmacological treatment of an acute migraine is aimed at shortening the attack and reducing severity. Nonspecific treatments include simple analgesics such as aspirin, paracetamol, non-steroidal anti-inflammatory drugs (NSAIDs), caffeine-containing agents and combination analgesics.[6] Narcotics should preferably be avoided as these mask the pain without suppressing the pathophysiological mechanism, leave the patient cognitively impaired, are addictive and exacerbate nausea.[8] Anti-emetic drugs facilitate absorption of the primary drug by increasing gastric motility and combat associated nausea and vomiting.

Specific treatment

Ergot derivatives ergotamine and dihydro-ergotamine (DHE) are non-selective agonists of $5HT_{1B/1D}$ receptors and are effective in the treatment of acute migraine. Main advantages include extended utilisation experience and low cost. Disadvantages relate to complex pharmacokinetics, lack of evidence regarding effective dose, potent and sustained generalised vasoconstrictor effects and high risk of overuse syndromes and rebound headache.[6]

Triptans on the other hand are selective agonists of $HT_{1B/1D}$ receptors. They have shown efficacy in well-designed trials with simple and consistent pharmacokinetics and well-established safety profiles. Use is however limited by high costs and vasoconstrictive complications in cardiovascular disease.[6]

There are three potential mechanisms of action of triptans:
- cranial vasoconstriction
- peripheral neuronal inhibition
- inhibition of transmission through second-order neurons of the trigeminovascular complex.

Sumatriptan was the first prototypal triptan. Unfavourable oral bioavailability and relatively short half-life inspired the search for similar compounds with superior pharmacokinetics. A number of second-generation triptans are available, including zolmitriptan, naratriptan, rizatriptan and eletriptan. Sumatriptan remains the only triptan available in injectable formulation and nasal spray, but both zolmitriptan and rizatriptan are available in rapidly dissolving formulations. The most frequent side-effects include tingling, paraesthesia, dizziness, flushing and neck stiffness. Cardiac symptoms may result due to coronary vasoconstriction and caution should be exercised when prescribing these drugs to patients with vascular risk factors. Triptans are therefore contraindicated in ischaemic heart disease, uncontrolled hypertension and cerebrovascular disease. The triptans have similar efficacy and safety profiles but differ in terms of tolerability.[3] Table I lists the pharmacological and clinical characteristics of oral triptans.

Selecting initial treatment can be difficult as migraine is a heterogeneous disorder. It is usually appropriate to initiate treatment with simple analgesics and then escalate treatment. However, in patients with significant disability it is appropriate to prescribe a triptan early.

Prophylactic treatment

The rationale for migraine prevention relates to the potential transformation into chronic persistent headaches despite the use of migraine-specific therapy. Transformation results over months to years resulting in daily, or nearly daily headache, similar to tension-type headache with superimposed migraine.[7] Risk factors for transformed migraine include:[8]
- analgesic overuse (30 - 80%)
- depression
- stressful life events
- alcohol abuse
- sleep disorders
- hypothyroidism
- hypertension.

The guidelines for preventive therapy proposed by the US Headache Consortium suggest that preventive therapy should be considered if any of the following criteria are met:[11]
- Migraine significantly interferes with the patient's daily routine despite acute treatment.
- Frequency of attacks is at least 3 per month with risk of acute medication overuse.
- Acute medication is ineffective, contraindicated, overused or results in

Table I. **Pharmacological and clinical characteristics of oral triptans, compared with 100 mg sumatriptan**

Drug and dose	Pharmaco-kinetic profile	Relief at 2h	Sustained freedom from pain	Consistency of effect	Tolerability
Sumatriptan					
50 mg	=	=	=	= or -	=
25 mg	=	-	= or --	-	+
Zolmitriptan					
2.5 mg	+	=	=	=	=
5 mg	+	=	=	=	=
Naratriptan					
2.5 mg	+	-	-	-	++
Rizatriptan					
5 mg	+	=	=	=	=
10 mg	+	+	+	++	=
Eletriptan					
20 mg	+	-	-	-	=
40 mg	+	= or +	= or +	=	=
80 mg	+	+ (+)	+	=	-
Almotriptan					
12.5 mg	+	=	+	+	+ +

= Similar value (associated with 100 mg sumatriptan).
- Inferiority (to 100 mg sumatriptan).
+ Superiority (to 100 mg sumatriptan).

Table II. **Comparative efficacy and safety of medications used for migraine prevention[11]**

Agent	Efficacy	Adverse events	Relative contraindication
Valproate	+ + + +	+ +	Liver disease, bleeding disorder
Topiramate	+ + + +	+ +	Kidney stones
Tricyclic antidepressants	+ +	+ +	Mania, urinary retention, heart block
Beta-blockers (propranolol)	+ + + +	+ +	Asthma, depression, Raynaud's disease, diabetes
Calcium-channel blockers (flunazine)	+ + +	+	Constipation, hypotension

troublesome adverse events.
- Patient preference.
- Presence of complicated migraine conditions:
  - hemiplegic migraine
  - basilar migraine
  - migraine with prolonged aura
  - migranous infarction.

The choice of prophylactic agent is often difficult and should be tailored to the specific needs of the patient. Selection of a specific class of drugs depends on patient profile and co-existing conditions.[7] In general, whatever agent is selected, drugs should be started at the lowest possible dose, increased slowly and given an adequate therapeutic trial of 3 - 6 months. If ineffective, or if unacceptable side-effects occur, consider an alternative agent.

The currently used preventive medications include beta-blockers (atenolol, propranolol), calcium channel blockers (verapamil), tricyclic antidepressants (amitriptyline, imipramine), selective serotonin re-uptake inhibitors and neuromodulators such as topiramate, gabapentin and valproate.[9] Other agents with lower level evidence include vitamin B_2, magnesium, botulinum toxin, neuroleptics, ACE inhibitors and NSAIDs. Table II compares the efficacy and safety of medications used for migraine prevention.

Beta-blockers and tricyclic antidepressants (TCAs) are often used as first-line therapy. Antiepileptic drugs (AEDs) may be appropriate first-line therapy in patients where beta-blockers and TCAs are contraindicated, such as asthma, congestive cardiac failure, orthostatic hypotension, cardiac conduction defects, depression, brittle diabetes or chronic fatigue syndrome and

in patients with co-morbid neurological or psychological disorders. AEDs appear to target one or more molecular sites in the brain with the ability to alter neurotransmission through their effects on ion channels, neurotransmitter receptors and neurotransmitter metabolism.[10]

FUTURE TREATMENT

Although the treatment of migraine has changed over the past decade due to an enhanced understanding of this complex headache, a substantial number of patients still find little or no benefit from available therapies. A crucial improvement will be acute treatment with agents that have exclusively neural action and thus fewer cardiovascular effects. Also drugs with novel mechanisms of action that act at different sites along the migraine pathway (e.g. CGRP antagonists) are currently under scrutiny.

Current prophylactic treatments are relatively nonspecific. Increased efficacy and tolerability of prophylactic drugs is required – after all, patients would prefer to have no migraine attacks at all.

References available on request.

IN A NUTSHELL

Migraine is the second most common cause of chronic daily headache.

Aura is characterised by transient cerebral ischaemia and spreading depression.

Mitochondrial disorders, magnesium deficiency and abnormalities in calcium channels may be responsible for neuronal excitability.

Activation of the trigeminovascular system and brainstem centres plays a pivotal role in the genesis of headache.

Non-pharmacological therapy includes changes in lifestyle and avoidance of triggers.

Nonspecific drug treatment includes simple analgesics aimed at shortening the attack and reducing severity.

Triptans are selective agonists of $HT_{1B/1D}$ receptors with 3 potential mechanisms of action: cranial vasoconstriction, peripheral neuronal inhibition and inhibition of transmission through the trigeminovascular complex.

The triptans have similar efficacy and safety profiles but differ in terms of tolerability.

Rationale for migraine prevention relates to the potential transformation into chronic persistent headaches.

Beta-blockers, TCAs and AEDs may all be appropriate first-line therapy.