Primary headache disorders: Focus on migraine

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SUMMARY POINTS

- Migraine is the most common disabling headache disorder.
- Most patients with disabling tension-type headache are likely to have migraine and accordingly respond to treatments efficacious in migraine.
- Individuals are genetically predisposed to experiencing recurrent migraine.
- Evidence supports migraine to be a primarily neural and not vascular mediated disorder.
- 1-2% of the population have chronic daily headache associated with acute-relief medication overuse; the majority are migraineurs.
- The presence of acute-relief medication overuse renders preventative medication less adequately efficacious.

Introduction

The International Headache Society classification for headache disorders provides a guide to diagnosing head and facial pain disorders. The classification is divided into two parts: primary and secondary headaches. The primary headache classification is supported by a healthy evidence base (1).

The primary headache classification is split into four sections: migraine, tension-type headache, cluster headache and other trigeminal autonomic cephalalgias, and other primary headaches. This article will focus on migraine - the most common disabling headache disorder.

Epidemiology

Migraine is globally the 12th most disabling medical disorder in women and 19th in men, as published by the World Health Organisation (2). The most disabling disorder in both sexes is

unipolar depression. The only painful disorder with greater disability than migraine is osteoarthritis, which is the 4th most disabling in women and 6th in men. The one year prevalence rate of migraine with or without aura in the UK is 7.6% in men and 18.3% in women (3). The prevalence varies by age and gender. Before puberty it is higher in boys than girls. The prevalence increases more rapidly in girls than boys into adolescence. Thereafter the prevalence increases in both sexes to peak at 40, and then declines (4). About one third of individuals will experience migraine with aura. Four to five percent of the population suffer from daily headache (5-7), and between 30 and 50% of these have a clinical syndrome which is consistent with migraine. One to two percent of the population have daily headache associated with medication overuse (6,8).

Clinical characteristics

There are a number of aspects to the migraine attack: the premonitory phase, headache, aura and recovery (9) (Table 1).

Table 1 International Headache Society classification criteria of migraine and tension-type headaches

Migraine	Tension-type headache
Episodic migraine (with or without aura*) <ul style="list-style-type: none"> • Unilateral (although often bilateral) • Pulsating • Moderate or severe pain intensity • Aggravation by or causing avoidance of routine physical activity • Nausea and /or vomiting • Photophobia and/or phonophobia 	Episodic tension-type headache <ul style="list-style-type: none"> • Bilateral • Non-pulsating/pressing/tightening • Mild or moderate but not disabling • No aggravation by or causing avoidance of routine physical activity • No nausea, vomiting, photophobia or phonophobia
Attacks last hours to days	Attacks last hours to days
Frequency 1-2 attacks/month	
Chronic migraine	Chronic tension-type headache
At least 15 headache days per month for >3 months with the above clinical description, in the absence of medication overuse.	
Chronic migraine is diagnosed two months after medication has been withdrawn without improvement.	
Medication-overuse headache Ergotamine, triptans or opioids taken on 10 or more days per month or 15 days for simple analgesics, for > 3 months.	
Typical aura symptoms* At least one of the following but no motor weakness: <ol style="list-style-type: none"> 1. Fully reversible visual symptoms including positive features (flickering lights, spots or lines) and/or negative features (loss of vision) 2. Fully reversible sensory symptoms including positive features (pins and needles) and/or negative features (numbness) 3. Fully reversible dysphasic speech disturbance At least two of the following: <ol style="list-style-type: none"> 1. Homonymous visual symptoms and/or unilateral sensory symptoms 2. At least one aura symptom develops gradually over ≥ 5 minutes and/or different aura symptoms occur in succession over ≥ 5 minutes 3. Each symptom lasts ≥ 5 and ≤ 60 minutes Additional loss or blurring of central vision may occur	

Premonitory symptoms

In a population based series up to 12% of individuals with migraine without aura experienced premonitory symptoms (10). Premonitory symptoms were reported by prospective electronic diary documentation. The most common symptoms were tiredness (72%), difficulty with concentration (51%) and a stiff neck (50%) (11). The most reliable predictors of an attack were yawning, difficulties with speech, difficulties with reading and increased emotion. Premonitory symptoms accurately predicted the onset of migraine headache within 72 hours 72% of the time.

Migraine headache

Table 1 gives the current International Headache Society (IHS) classification criteria for migraine without aura. In about 60% of patients the headache is unilateral (12). Whether unilateral or bilateral, the pain is predominantly in the distribution of the first division of the trigeminal nerve. Most commonly the pain tends to be frontotemporal and periorbital, often spreading to the parietal and occipital areas. A quarter to a third of patients experience pain in one or both regions of the occiput and neck (13,14). The relevance of this is paramount. It is not infrequent that the cervical spine is erroneously implicated in generating the pain in primary headache disorders. However involvement of regions of the occiput and neck are consistent with the physiological nociceptive connections which

subserve the head and neck. Functionally the trigeminal nucleus extends beyond the traditional nucleus caudalis to the dorsal horn of the high cervical region. The sensory innervation of the superior sagittal sinus is mainly from the ophthalmic first division trigeminal. In the cat stimulation of either the superior sagittal sinus, or the greater occipital nerve (C2), results in increased metabolism in both the trigeminal nucleus and the dorsal horn at C1 and C2 (15). In human volunteers local anaesthetic block of the greater occipital nerve results in modulation of the ipsilateral nociceptive blink response (16). This is the basis for the therapeutic success of occipital nerve blockade (17) and neurostimulation (18) in headache.

A prolonged attack of migraine lasting more than 72 hours has been termed *status migrainosus*. This is an arbitrary definition, predating the recognition of chronic migraine and medication-overuse headache (19). In the majority the pain is pulsating, in the remainder the pain is described as pressing or tightening. Aggravation of the headache by routine physical activity is a very sensitive feature of migraine headache and occurs in over 95% of sufferers (10,12). The median attack frequency (about 70% of migraineurs) is one to two attacks per month. Several population-based studies have found a positive correlation between pain severity and the occurrence of associated symptoms (20), distinguishing the disorder from tension-type headache.

Recovery

In most patients the headache resolves gradually. Some patients find that sleeping for a few hours will abolish the headache. Other patients find that vomiting will arrest an attack (21). Even after the headache has resolved, many patients do not feel entirely back to normal for some time. In one series, 47 of 50 patients remained symptomatic after the headache had ended (22). The most frequent symptoms were changes in mood (72%), asthenia (54%), tiredness (52%) and reduced appetite (32%). The average duration of these symptoms before complete resolution was 23 hours.

Aura

Table 1 gives the current definition of typical aura. Although aura is most commonly observed with migraine, it is not specific to migraine and can occur with all primary headache disorders (23-25). Visual aura is most common, occurring in over 90% of cases of aura (26). From a population based study sensory (31%), aphasic (17%) or motor (6%) aura are less common and usually occur with visual aura. The aura is of gradual onset and progression, and lasts less than an hour in 70-80% of individuals. In most patients the aura precedes headache, which follows within the hour. However the headache can occur simultaneously with the aura, before the aura (27) or several hours after the aura (28).

Motor weakness is the least common aura symptom and occurs in hemiplegic migraine, of which there is a recognised familial and sporadic form. Familial hemiplegic migraine is rare and inherited in an autosomal dominant manner; the estimated prevalence is 0.01%. Motor aura usually last more than an hour. There are usually additional sensory symptoms in the same distribution (98%): visual aura (89%), aphasia (72%) and basilar-type symptoms (69%) (29). A diagnosis of basilar-type migraine is given to aura originating from the brainstem or both cerebral hemispheres, but *without* motor phenomena. Most commonly experienced symptoms are vertigo, dysarthria, tinnitus, diplopia and bilateral visual symptoms. Less commonly bilateral paraesthesias, decreased level of consciousness, hyperacusis and ataxia can occur.

Chronic migraine

A diagnosis of chronic migraine is made with at least 15 headache days per month for more than 3 months. The phenotype is of migraine without aura in the absence of medication overuse. Medication-overuse is defined as ergotamine, triptans or opioids taken on 10 or more days per month, or 15 days for simple analgesics. A diagnosis of chronic migraine can be made if the patients continues to experience at least 15 headache days a month two months after acute-relief medication withdrawal (1)(Table 1).

Migraine and tension-type headache

Migraine is clinically heterogeneous within and across individuals. Individuals with migraine can experience a different combination of symptoms, often related to severity, and at different periods in their life time. For example, some attacks may be mild, with mild nausea or photophobia only. If untreated this attack may escalate into a typical migraine headache as per definition. Epidemiological and experimental evidence suggests that these milder headaches,

which are often defined as tension-type headaches, are biologically migraine headaches (30-32). In a study of 432 patients the accuracy of initial headache diagnosis assigned by a clinician was compared to that made by a neurologist after diaries detailing 10 attacks (30). This showed that disabling tension-type headache is rare. Patients initially diagnosed with disabling tension-type headache were reclassified as migraine headache or probable migraine headache. Probable migraine headache is defined as an attack fulfilling all but one of the criteria in Table 1. The importance of this is paramount: patients who are misdiagnosed remain mismanaged.

Pathophysiology

Migraine is no longer considered a primarily vascular disorder. This tenet was based upon the work of Wolff and colleagues who showed that the main pain sensitive structures in the brain were vessels (33); vasodilatation could cause pain (34) and therapeutic drugs such as ergotamine, and hence the triptans, were vasoconstrictive (35). Since that time studies have shown that the pain and vasodilatation do not necessarily correlate temporally (36), nor in existence (37). Patients can experience typical attacks of headache responsive to treatment with sumatriptan, without vasodilatation (38). It is much more plausible that the efficacy of ergotamine and the triptans is related to the ability of these drugs to inhibit nociceptive signaling at peripheral trigeminal afferents (39) and centrally (40,41). This is further supported by functional imaging studies demonstrating the involvement of central brain structures integral to nociception (42,43).

Migraine attacks are largely experienced episodically. During this time, and often between attacks, individuals have a heightened perception of various sensory modalities. As defined by the syndrome, there is particular sensitivity to light, noise, and often smell and movement. Conceptually concordant with migraine as an episodic disorder of brain excitability is the identification of three pathological genes in familial hemiplegic migraine (FHM). The FHM1 gene (CACNA1A) encodes the pore-forming alpha-1A sub-unit of P/Q-type voltage-gated neuronal calcium channels. There are over 50 mutations associated with a range of phenotypes which include episodic ataxia type 2 and spinocerebellar ataxia type 6. FHM2 is associated with mutations in the ATP1A2 gene which encodes the alpha-2 subunit of sodium-potassium pump ATPases. ATP1A2 mutations have been associated with a range of clinical phenotypes of FHM with and without cerebellar ataxia, basilar-type migraine and epilepsy. FHM3 is associated with abnormalities in the SCN1A gene which encodes the alpha-1-subunit of neuronal voltage-gated sodium channels. A wealth of mutations in this gene have been associated with epilepsy syndromes (44).

The genetics of the more common forms of migraine with and without aura have been less forthcoming. However Lafrenière and colleagues recently reported a mutation in the KCNK18 gene that interrupts TRESK (TWIK-related spinal cord potassium channel) function in one large family with migraine with aura (45). The authors showed prominent TRESK expression in migraine-

salient areas such as the trigeminal ganglion. The mutation causes production of an incomplete form of TRESK which disrupts the normal functioning of the protein, resulting in neuronal excitability.

The functional consequences of these genetic mutations remain key to understanding the details of migraine pathophysiology.

Management of migraine

Throughout management patients should keep a daily headache diary documenting attack frequency, disability, acute attack treatment use and - in women - menstruation. Where relevant, preventative treatment use should be documented and all concomitant medication listed. This focuses the patient on their management and provides invaluable information to the clinician on how best to manage the disorder. This information is summarised in Table 2.

Management of aggravating factors

Individuals with migraine will experience times when they are more or less susceptible to experiencing headaches, spontaneously and in response to a number of exogenous and endogenous factors. Typical triggers include a missed meal, too little or too much sleep, alcohol, stress and less commonly the immediate post-stressful period, weather changes and sensory stimuli (usually visual and olfactory) (46-48). Dietary triggers are overestimated; few individuals have

specific dietary triggers. Dietary manipulation may result in headache improvement but this appears to be regardless of the diet used (49). Caffeine and analgesics are the most surreptitious of the aggravators. Thus tea, coffee and caffeinated soft drinks should be minimised and the frequency of use of acute-relief medication restricted (50,51).

A specific trigger will not consistently predispose an individual to experiencing a migraine attack. This fact is most likely to be due to inherent variability in the way the migrainous brain functions. Thus, minimising the contribution of such a trigger to the disorder is best achieved by routine in daily activities, rather than complete avoidance: e.g. regular sleeping and meal times, modification of alcohol and caffeine intake.

Hormonal triggers

About 50% of female migraine sufferers experience troublesome migraine headaches associated with menstruation (46-48). Migraine can worsen in the first trimester of pregnancy but improve thereafter. The menopause, oral contraception and hormone replacement therapy can be associated with worsening, improvement or no change in the disorder. Unfortunately outside the context of strictly defined menstrual migraine, hormonal manipulation, either medical or surgical (i.e. oophorectomy) has not complemented the therapeutic armoury in migraine (52).

Table 2 Preventative medication in the treatment of migraine European Federation of Neurological Societies guidelines (53)

Preventative treatment	Daily dose
Established as effective	
Propranolol	40-240mg
Metoprolol	50-200mg
Flunarizine*	5-10mg
Sodium valproate	500-1800mg
Topiramate	25-100mg
Probably effective	
Amitriptyline	50-150mg
Bisoprolol	5-10mg
Possibly effective	
Aspirin	300mg
Gabapentin	12-1600mg
Magnesium	24mmol
Riboflavin	400mg
Coenzyme Q10	300mg
Candesartan	16mg
Lisinopril	20mg
Methysergide	4-12mg
Pizotifen	0.5-4mg
*Flunarizine is not licensed in the UK but can be obtained on a named-patient basis	

**Table 3 Acute treatment in migraine management
European Federation of Neurological Societies guidelines (53)**

Acute treatment	Route	Dose
Aspirin	Oral or intravenous	1000mg
Ibuprofen	Oral	200-800mg
Naproxen	Oral	500-1000mg
Diclofenac	Oral	50-100mg
Paracetamol	Oral or rectal	1000mg
Aspirin	Oral	250mg
+ Paracetamol	Oral	200-250mg
+ Caffeine	Oral	50mg
Acute treatment	Route	Dose
Almotriptan	Oral	12.5mg
Eletriptan	Oral	20-40mg
Frovatriptan	Oral	2.5mg
Naratriptan	Oral	2.5mg
Rizatriptan	Oral (+wafer)	10mg
Sumatriptan	Oral	25, 50, 100mg (+rapid release)
	Intranasal	10, 20mg
	Subcutaneous	6mg
Zolmitriptan	Oral (+dispersible)	2.5, 5mg
	Intranasal	2.5, 5mg

A meta-analysis of 53 clinical trials compared the triptans to sumatriptan 100mg. Rizatriptan 10mg showed better efficacy and consistency, with similar tolerability. Eletriptan 80mg showed better efficacy, similar consistency but lower tolerability. Almotriptan 12.5mg showed better efficacy but better consistency and tolerability. Zolmitriptan 5 and 10mg, Eletriptan 40mg and Rizatriptan 5mg showed similar results. Naratriptan 2.5mg showed lower efficacy but better tolerability. Data on Frovatriptan was not available (54).

Acute-attack management

Acute-attack treatments can be divided into two groups: non-specific and headache specific treatments. The former includes simple analgesics and the latter the triptans and ergot alkaloids. Currently available ergot alkaloids have been largely relegated to history in the UK, but can be effective if used cautiously in selected patients. Generally, unless attacks are infrequent, paracetamol and opiate based preparations should be avoided, and the use of non-steroidal anti-inflammatory drugs (NSAIDs) preferred (53) (Table 3). The basis for this lies in the wealth of data which implicate the former more frequently than the non-steroidals in medication overuse headache.

Although medication overuse headache with the triptans and ergotamine alkaloids is well established, the withdrawal from analgesics is more protracted (50). An ergotamine alkaloid or triptan should be reserved for patients with more disabling attacks. The choice of triptan will be governed by more factors than efficacy, for example: consistency, recurrence, side effect profile and route of administration.

In patients where a single acute agent has proven inadequately effective, combination therapy can be considered. A randomised placebo-controlled trial of sumatriptan 85 mg and naproxen sodium

500 mg showed benefit of the combination compared with either monotherapy, with a well-tolerated adverse event profile (55).

Approach to treatment of the acute attack

Realistically a reduction of pain from moderate or severe, to mild or none at two hours is the end-point adopted by most recent acute treatment trials. If no response is obtained at two hours, repeat dosing with the same drug and/or dose has not shown to be effective (56,57). Treatment should be escalated to a higher dose or different treatment. The response across three attacks has been taken to give a measure of consistency. Two from three failed responses to the maximum tolerated dose of a treatment should prompt progression to an alternative drug. Recurrence within 24 hours after successful initial treatment can be re-treated with the same effective strategy used earlier in the attack.

Selection of the most appropriate treatment based upon assessment of attack severity appears to be more cost effective than a stepped approach of, for example, first trying a non-steroidal and if ineffective moving on to a triptan (58).

It is not always easy to know which attacks will escalate into a more severe migraine attack. This is further complicated by clinical trials which show better outcomes when attacks are treated when mild, rather than when moderate (59); therein lies the potential

for medication overuse. This may, however, be restricted to the oral preparation. There is no significant difference in response rates of attacks treated when mild or severe with subcutaneous sumatriptan (60). The alternative is that individuals restrict acute-relief medication use to a fixed number of days a month when they have planned commitments, allowing those days when no activity is planned to be managed non-medically.

Medication overuse has not been reported for an acute-relief medication taken on eight or less days per month. Thus this would be the advised restriction of acute-relief medication use. It is the frequency of use and not the dosing which is relevant. For example, one paracetamol tablet a day is much more likely to cause medication overuse than eight tablets taken on one day in the week (61). A personal preference is to restrict the use to six days, given that there may be months when some individuals find it hard to restrict the use, which may then escalate inadvertently. If it does so, to eight days in a month, then at least throughout they have maintained acute-relief medication restriction, thereby minimising any risk of medication-overuse headache.

Triptans taken pre-emptively during the aura phase are safe but do not prevent the headache phase of the attack (62).

Nausea and vomiting are common in migraine attacks. During migraine there is gastric stasis which delays oral drug absorption (63). Metoclopramide 10mg orally or intramuscularly has been shown to be effective in the pre-emptive treatment of migraine attacks, improving the absorption and efficacy of acute treatments (64). An alternative option is domperidone, 10-20mg orally or 60mg rectally (65).

Medication overuse

The question of whether medication overuse is the cause of worsening of the migraine disorder or merely a symptom has not been clearly defined, but is inferentially assumed.

The prevalence of chronic daily headache (CDH) was observed in 105 rheumatology patients attending a monitoring clinic using one or more regular analgesics for the arthritis (66). Of this group six experience a CDH phenotype consistent with chronic migraine and two with tension-type headache. All gave a past history of migraine. The onset of migraine headache occurred before the onset of CDH in seven and at about the same time as the CDH in one patient. In all but one, the use of analgesics preceded or occurred around the same time as development of CDH. Similarly in cluster headache, only patients with a past or family history of migraine develop a chronic daily headache, with migraine or tension-type headache phenotype, whilst taking daily sumatriptan acutely (67).

Thus, acute-relief medication only seems to cause medication-overuse headache in individuals with a migrainous predisposition.

There is only placebo controlled study for caffeine (51). It shows that when regular consumption of caffeine suddenly ceases and is replaced by placebo, at day two the individual experiences a worsening of their headaches ('rebound'). This period lasts about 10 days. Over the following about three weeks, there is gradual improvement back to the individual's inherent pattern of migraine attacks. The same sequence of events is seen with all acute-relief medications. Notably, the time to improvement can be 6-12 weeks (68).

In a prospective study of 216 patients, at eight weeks 47% were improved, 48% no different and 7% were worse. Of the 47% who still required further improvement and were established on preventative therapy, former non-responders had a 49% decrease in headache frequency. Those who had never received prophylaxis had a 56% reduction (69). Thus the key issue here is that *preventative efficacy is diminished in the presence of medication-overuse*.

Various strategies used for supporting medication withdrawal have been used, from outpatient withdrawal to inpatient detoxification programmes, delay or immediate introduction of preventative therapy. Evidence suggests that there is no difference in outcome across the different approaches (70). One of the poor prognostic indicators for chronic migraine is medication overuse (71). Behaviour rather than severity of the disorder seems to drive the

Table 4 Management of migraine

Evaluation of the disorder by diary documentation.
Address life-style triggers such as sleep pattern, missed meals, stress and caffeine use.
If ≥ 4 headache days/month which require treatment, optimise acute attack treatment according to disability of attack. Non-steroidal anti-inflammatory $\pm$ anti-emetic $\pm$ triptan.
If ≥ 4 headache days/month which require treatment or do not respond to acute treatment – introduce preventative treatment. Use of latter will depend on medical co-morbidities and discussion of adverse event profile with patients.
Optimise preventative treatment balanced by efficacy and adverse event profile.
Always restrict acute relief medication use to a maximum of 8 days/month to avoid medication overuse headache.
In patients with medication overuse headache ensure non-pharmacological support through a health psychologist. Patient may chose abrupt or tapered withdrawal. The majority of patients will need establishment of preventative treatment for a period of time.
Tailor preventative treatment according to the activity of the disorder.
Ensure diary documentation and optimisation of lifestyle factors throughout.

process. Thus supportive non-pharmacological approaches should be integral to management (72).

Preventative treatment

Individuals experiencing four to five disabling headache days each month, which require treatment, should be considered for preventative therapy. The number of headache days is somewhat arbitrary but serves to prompt a re-evaluation in the management strategy of an individual who may otherwise begin to venture into the realm of medication overuse headache. As with many disorders, it remains a matter of trial and error to find a preventative measure which is effective and tolerated. The importance of achieving adequate preventative doses cannot be emphasised enough. Avoidance of adverse effects with the aim of achieving this goal is best achieved by increasing the drug slowly at small increments.

Lack of effect at the maximum tolerated dose should prompt withdrawal and trial of another drug. A partly effective dose may be reached, but with intolerable adverse effects at higher doses. In this situation a second drug can be added. This may be with a view to achieving monotherapy once established, or combination therapy at lower and tolerated doses.

The objective is to achieve good symptom control for at least 6-12 months before gradually withdrawing the preventative medication to see whether the symptoms have naturally improved. If this is not the case the drug should be increased back up to the dose with which symptomatic improvement is maintained again. Withdrawal can be tried again 6-12 months later. Table 2 gives a list of preventive medication in the treatment of migraine headache.

Secondary migraine

The migraine attack is a clinical syndrome. This is quite different from the disorder of migraine as discussed in this article. The latter is an inherent (genetic) predisposition to recurrent migraine attacks which are benign, albeit disabling. The current data suggest that in patients who present with typical migraine with or without visual aura, the yield of associated pathophysiology is so small that routine imaging is not warranted (73). However, a migraine attack can be precipitated by a secondary pathology. This is well reported and examples include post-trauma (74), subarachnoid haemorrhage (75), stroke (76), venous sinus thrombosis (77), meningitis (78) and encephalitis (79). In the case of subarachnoid haemorrhage the patient responded to sumatriptan, whereas two patients with meningitis did not respond (78). In these cases the headache was either of new onset or recurrent on a past history. It was not the clinical syndrome which aided the diagnosis, but acute onset headache, systemic ill-health, or additional neurology.

Summary

Migraine is a disorder experienced by those with genetic susceptibility. There is increasing aetiological evidence for dysfunction of central nociceptive functions, rather than primarily vascular phenomena. The disability associated with migraine is well recognized by the World Health Organisation, yet less well accepted in day-to-day practice. Chronic migraine contributes significantly to this disability. About 2% of the population has chronic migraine with medication overuse. The latter has been reported for all groups of acute-relief medication used on more than eight days a month. Non-steroidal drugs are the least implicated, although this may simply be prescription bias. Triptans have the most rapid time, lowest dose and frequency of use prior to development of medication-overuse headache. However, they remain the most effective acute treatments. Notably medication-overuse renders prophylaxis less efficacious. Thus, pre-emptive therapy requires vigilant monitoring of headache frequency with early introduction of adequately dosed preventative treatment. The inherent variability in activity of the disorder should be addressed by managing typical avoidable triggers, such as lack of sleep or missed meals. Adequately dosed acute treatment should be restricted to maximum eight days a month. There should be early introduction of preventative treatment once the attacks frequency reaches 4-5 headache days a month requiring acute treatment. The management of migraine is summarised in Table 4.

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