Migraine in people with epilepsy: a treatable and neglected co-morbidity

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Abstract

Migraine and epilepsy account for more than 40% of neurology outpatients and are leading causes of disability [1]. They often co-exist and can be confused, because of shared clinical features. The borderlands and links between migraine and epilepsy have fascinated neurologists for centuries, and unresolved questions remain. Greater understanding of the relationship between migraine and epilepsy may give insight into shared mechanisms. It is already clear that treating co-existing migraine is an important therapeutic opportunity and may improve epilepsy [2].

Definitions

There are no specific biomarkers for epilepsy or migraine. Outpatient studies suggest the diagnosis of epilepsy is accurate in about 2/3 of cases [3], and migraine definitions are subjective. Revised definitions of epilepsy emphasise the chance of seizure recurrence, combining clinical and investigation features [4]. The International Headache Society definition aims for clarity, presenting migraine as an episodic headache lasting 4-72 hours. The definition requires two of the following: worsened by movement, unilateral, throbbing, moderate or severe; and either nausea and/or vomiting or photophobia and phonophobia [5]. This rigid definition misses much of the migraine encountered in clinical practice [6]. The distinctions between migraine and tension headache are also blurred, meaning that some migraine associated with epilepsy is mislabelled as tension headache. Migraine may recur with no headache or may simply be an aura, and pain may be in the abdomen or limbs, particularly in children [6,7]. Earlier definitions of migraine were more fluid, and arguably more reflective of real life – "recurrent attacks of headache widely varied in intensity, frequency and duration...commonly unilateral in onset; are usually associated with anorexia, and sometimes with nausea and vomiting; and some are proceeded by, or associated with, conspicuous sensory, motor, and mood disturbances; and are often familial" [8]. A key feature of migraine is hypersensitivity to sensory stimuli between as well as during episodes. There may be autonomic, motor, cognitive, psychic and sensory features as well as the headache [6].

Shared clinical features

Similarities between migraine and epilepsy in triggers, prodrome, aura, features of the ictus, and treatment demand careful analysis to avoid confusion.

Triggers

Alcohol withdrawal is a trigger for an estimated one-fifth of seizures, usually occurring 6-12 hours after imbibing (usually >7 U) and predominantly in genetic generalised epilepsy [9]. Alcohol-induced migraine (veisalgia or "hangovers") as well as acute sensitivity, particularly for red wine, are well recognised in migraineurs [10]. For migraine and epilepsy, sleep and food deprivation, as well as stress and relaxation may be individual triggers. With regard to visual stimuli, photophobia is a feature in 80% of people with migraine in at least some attacks [6]. In epilepsy only 5% of patients have photosensitivity or photoconvulsive seizures [11].

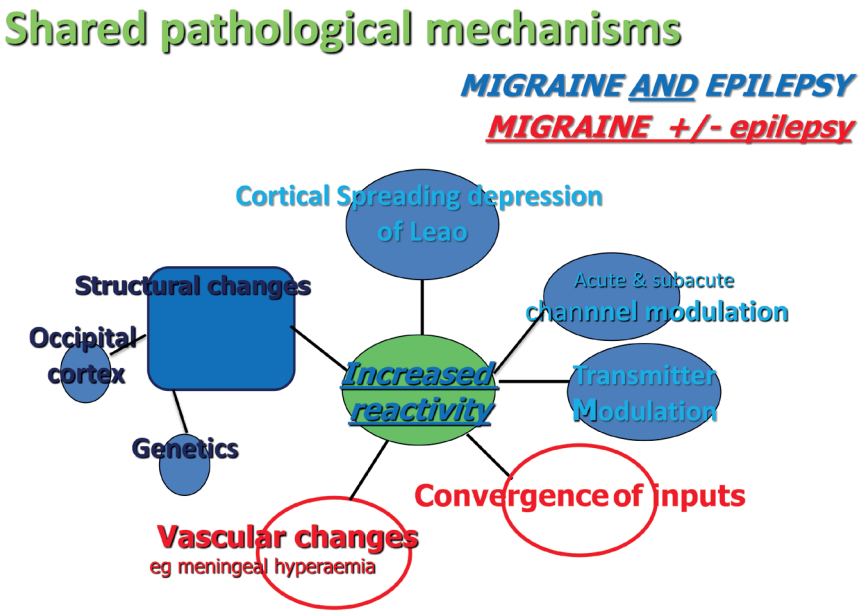
Prodrome

30-90% of people with migraine have a prodrome [12] manifestating heightened sensitivity to sensory stimuli. 6-40% (average 30%) of people with epilepsy report a prodrome, including heightened sensitivity, changes in cognition, mood or appetite, and a migraine headache in 8% [13].

Aura

Migraine aura may occur without a headache, or before, during or after one, and may be positive (such as tingling) or negative (for example hemiplegia) [6]. In epilepsy, aura (now denoted focal aware seizures) are usually positive phenomena and occur as the seizure manifestation or at seizure onset. Some aura features are similar – this is particularly important for visual, gustatory and olfactory sensations. Duration and evolution is the most important distinction – epileptic aura are usually brief with sudden onset and offset, migraine aura usually evolve and recede, lasting many minutes [6,14].

Elementary visual hallucinations are the most common migraine aura – usually linear, monochrome, 5-30 minutes duration, with gradual onset and offset [14]. They are usually distinguished from the occipital epilepsy aura, characteristically less than 2 minutes duration, rapid in onset and offset, coloured and circular [14]. Complex visual hallucinations are rare in both migraine and epilepsy and alternative diagnoses should always be considered [6,14]. Olfactory hallucinations, usually brief and unpleasant, occur in 1-66% of those with temporal lobe epilepsy [15]. They also happen in migraine, lasting between 5 minutes and 24 hours, and may be misdiagnosed as epilepsy [16]. Similarly, brief, unpleasant elementary gustatory hallucinations are well docu-



The figure models shared pathological mechanisms for migraine and epilepsy. Blue represents shared mechanisms of migraine and epilepsy. Red represents mechanisms unique to migraine.

Table I: Differentiating auras in migraine and epilepsy

Differentiating auras in migraine and epilepsy		
	Migraine	Epilepsy
Onset	Gradual – minutes	Sudden
Offset	Gradual – minutes	Sudden
Duration	Minutes to hours	Seconds to minutes
Relation to ictus	Before, during, after OR without headache	Before unaware seizure OR without unaware seizure
Allodynia	Common	Never
Visual aura	Common linear, monochrome	Rare, circular, coloured

mented in temporal lobe epilepsy but also occur in migraine. Elementary auditory hallucinations (tinnitus) are a frequent migraine aura [6]. Vestibular hallucinations (vertigo or disequilibrium) occur in 30-50% of people with migraine [17], typically lasting minutes or hours. The frequency of auditory and vestibular hallucinations in epilepsy is uncertain.

Autonomic features occur in more than 80% of migraine [5-7], usually lasting for hours, most commonly vomiting, pallor or sweating. In epilepsy they are uncommon, except in childhood occipital epilepsy and temporal lobe epilepsies. A brief epigastric aura occurs in up to 27% of people with temporal lobe epilepsy [18].

Somatosensory aura, usually tingling, is frequent in migraine. As clinical examination is normal it is often misdiagnosed as functional [6]. In migraine, head pain is present during at least some episodes in most cases. Variants include abdominal migraine or limb pain (periodic syndromes), particularly in children; but in 1-2% of adult migraine sufferers [19,20]. Ictal pain is reported in <3% of seizures [21,22], usually parietal or temporal lobe onset and most common with head, abdominal or limb pain reported, of duration from seconds to 30 minutes, and variable intensity [21]. Allodynia is a key distinguishing feature as it is not present with epilepsy, but is present in 40-60% of people with migraine [23].

Prevalence

Overall population incidence of migraine is 10%, but 50-80% in neurologists and headache specialists [24], at least partly due to heightened awareness. Migraine is primary, with a family history in about 70% [5]. The epilepsies are a collection of different conditions, occurring in 1% of the population, with established aetiology in about half, and genetic factors increasingly recognised [25]. Migraine is more common in people with epilepsy (and vice versa), estimated as 8-33% in unselected epilepsy populations with variable study design making meta-analysis problematic [2,26] and higher in those with catamenial epilepsy and migraine with aura [2]. Incidence of migraine varies with epilepsy subtype, occurring in 75% of people with occipital epilepsy [14].

Peri-ictal headache & interaction with epilepsy

There is no evidence that migraine causes epilepsy or vice versa [27] but peri-ictal headache is common and undertreated. Migraine may precede or follow a seizure, again arguing against a causal link. Migralepsy (or migraine-triggered seizures, the newer but clumsier term) [5], is described as classic visual aura followed by a seizure occurring within an hour of the aura [28]. Although controversial, it has been demonstrated electrographically in a few cases, and described convincingly in others. Marks and Ehrenberg [2] recorded the entire sequence from migraine aura to partial seizure in two patients with distinctive changes on the EEG during the migraine aura preceding the onset of an electrographic seizure. In five other patients, periodic lateralised epileptiform discharges were recorded in close temporal relation to their migraine attacks. Childhood occipital epilepsies have migrainous features at onset, and arguably represent a form of migralepsy [14]. Complicating interpretation, EEG changes occur in up to 43% of migraineurs (usually non-specific delta and theta waves, but occasionally spike-and-wave) [29]. This highlights the hazards of requesting an EEG in people investigated for syncope with co-existing migraine.

Ictal headaches are rarely described – hemicrania epileptica and epileptic headache are defined by epileptiform EEG changes [30], and as EEG is rarely recorded during migraines, the exact incidence is unknown.

Postictal headache is reported in 31-56% of patients after a tonic-clonic seizure but not after absence seizures [31,32]. 50-70% of sufferers have interictal migraine and 6% have pre-ictal headache. These headaches usually fulfil criteria for migraine [31].

Treatment of peri-ictal and inter-ictal migraine

Treating migraine in people with co-existent epilepsy and migraine potentially improves both conditions. In 6/79 (8%) of patients with refractory epilepsy, adding anti-migraine treatment to ASMs improved seizure control [2].

There are no randomised controlled trials specifically investigating treatment of migraine associated epilepsy. Some antiseizure medications (ASMs) work for both migraine and epilepsy. Topiramate and valproate have class I evidence for efficacy in both conditions [33]. Of other drugs with efficacy in epilepsy, levetiracetam, lamotrigine, gabapentin and pregabalin have also been trialled for migraine but without conclusive evidence of efficacy [34]. Most of the standard migraine treatments are suitable for people with epilepsy, and considerations are summarised in the Table 2. Whether to try to treat both conditions with a single medication, or separately, is a matter of individual clinical judgement tailored to the individual's lifestyle, co-morbidities and treatment preferences.

Table 2: Treating migraine in people with epilepsy

Medication	Efficacy in migraine	Considerations if used in people with epilepsy & migraine
Acute treatments		
Aspirin	High	Potential for metabolic acidosis with ZON, TOP & ACZ
Triptans	High	Nil known interactions
2nd generation Gepants	Less effective than triptans	Gepant levels reduced by phenytoin, phenobarbitone, less reported cardiovascular adverse events than triptans
Preventive treatments		
Beta blockers	High	No significant interactions
Tricyclic antidepressants	High	Small risk of increased seizures
Angiotension blockers	Moderate-high	No significant interactions
Aspirin	High	Potential for metabolic acidosis with ZON, TOP & ACZ
CGRP antagonists	High	No reported pharmacokinetic interactions
Botulinum toxin	Moderate-high	No significant interactions
External stimulators	Low	No significant interaction
Neuromodulation	Low	No significant interaction
ASMs repurposed as migraine preventive treatments		
Topiramate	High	Not for PPC
Valproate	High	Not for PPC
Gabapentin	Very low – same efficacy as placebo	Not effective for migraine
Pregabalin	Very low	Not effective for migraine
Levetiracetam	Low	Not effective for migraine
Lamotrigine	Low – same efficacy as placebo at 12/52	Not effective for migraine
Carbamazepine	Low	Not effective for migraine

ASMs = Anti-seizure medications, ZON = Zonisamide, TOP = Topiramate, ACZ = Acetazolamide, PPC = People potentially conceiving

Shared mechanisms

Links between migraine and epilepsy are indirect. Shared pathological factors include structural changes in the occipital cortex, genetic changes particularly channelopathies, cortical spreading depression of Leão [14,32] and acute and sub-acute channel and transmitter modulation [14]. Specific transmitter changes in the occipital cortex may have a role, with increased glutamate-to-glutamine ratio reported in women with migraine, and high neuron-to-astrocyte ratio, with these neurons containing the high glutamate-to-glutamine ratio [14,32]. Astrocytes, important in the reversal of the changes of cortical spreading depression are less in occipital cortex [14]. Trauma may cause epilepsy through glutamate receptor activation, excitotoxicity and hypersynchrony, changes which can also trigger migraine [14]. Rare monogenic channel defects produce both migraine and epilepsy [35]. Convergence of inputs and vascular changes, particularly meningeal hyperaemia are important mechanisms in migraine, little studied in epilepsy [36,37]. Analysis of the mechanisms of the two ASMs with proven efficacy in migraine does not resolve pathogenesis, due to their multiple mechanisms of activity. Topiramate changes GABA, AMPA, sodium channels and calcium channels, and sodium valproate increases GABA, enhances GABA response, increases potassium conductance and reduces neurogenic inflammation [33].

Conclusions

Careful clinical assessment usually allows differentiation of the shared features of migraine and epilepsy. Migraine is a common co-morbidity for people with epilepsy, occurring in more than 20% of people with epilepsy overall, and 75% in people with occipital lobe epilepsy [14]. It is most commonly post-ictal, but may also be prodromal, pre-ictal, or ictal. Most migraine therapy can be used safely in people with epilepsy. Pro-active treatment of co-morbid migraine reduces an unnecessary burden for people with epilepsy, and may directly improve their epilepsy [2].

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