MIGRAINE AND EPILEPSY

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ABSTRACT

The association between migraine and epilepsy is complex and bi-directional. In migraine and epilepsy transient neurological symptoms, normal neurological and physical findings between events and genetic/familiar disposition are common.

Recent basic research findings revealed pathophysiological links between migraine and epilepsy. Also, epidemiological studies suggested that the occurance of migraine and epilepsy in an individual could be beyond changes.

Comorbid conditions may create therapeutic opportunities, antiepileptic agents like divalproex sodium and topiramate may prevent attacks of both migraine and epilepsy.

Key words: migraine, epilepsy, anticonvulsant medication

INTRODUCTION

The realationship between migraine and epilepsy has intrigued neurologists for more than a century. Occurance of both diseases in the same patient is seen by some authors as a chance association, but many other experts consider that there may be common pathogenesis aspects.

Migraine is a common, chronic disorder characterised by episodes of severe headache (often throbbing and frequently unilateral), associated with autonomic nervous system dysfunction (nausea, vomiting) and with sensitivity to afferents, such as light, sound and head movement **(migraine without aura**).

Approximately 30% of migraine sufferers experience aura – transitory visual or sensorio-motor dysfunction that precedes or accompanies the headache **(migraine with aura).**

In migraine, as well as in epilepsy, transient neurological symptoms, normal neurological and physical findings between events and genetic/familiar disposition are common.

CLINICAL FINDINGS

Aura in migraine and in epilepsy

Migraine and epilepsy are characterised by episodes of neurological dysfunction. It is difficult to **differentiate migraine with aura from partial complex seizure**.

- If the aura is brief (<5 minutes) and associated with alteration of consciousness, automatisms and another positive motor features (tonic-clonic movements), epilepsy is more likely.
- If the aura is of long duration (> 5 minutes) and has a mix of positive (scintillations, tingling) and negative features (visual loss, numbness), migraine is more likely.

Occipital lobe seizures are characterised by positive and negative visual phenomema. Positive phenomena include elementary visual hallucinations often described as bright lights or colored lights – unlike the more complex visual hallucinations of posterior parietal or posterior temporal lobe origin. Negative phenomena include amaurosis, scotomas and hemmianopsia. The visual phenomena usually are contralateral to the side of seizure and may remain stationary or move across the field. Postictally – perisitent amaurosis (hours) may occur.

Other occipital seizure manifestations include tonic and clonic eye deviation, head deviation, blinking, nystagmus. Eye and head deviation aree contralateral to the side of the seizure focus.

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According to Panayiotopoulous, idiopathic occipital epilepsy with visual seizures and migraine aura coulde be differentiated on clinical grounds. In epilepsy ictal elementary visual hallucinations are stereotyped for each patient, usually lasting for seconds. They consist of mainly multiple, bright coloured, small circular spots, circles, or balls. Mostly, they appear in a temporal hemifield often moving contralaterally or in the centre where they may be flashing. They may multiply and increase in size in the course of the seizure and may progress to other non-visual occipital seizure symptoms and more rarely to extra-occipital manifestations and convulsions. Blindness occurs usually from the beginning and postictal headache, often indistinguishable from migraine, is common. So, elementary visual hallucinations in occipital seizures are entirely different from visual aura

Typical migraine aura is characterised by gradual development, with a duration longer than 1 hours, with a a mix of positive and negative features and is completely reversible.

Visual aura is the most common type of aura, often presenting as fortification spectrum – *zigzag* figure near the point of fixation that may gradually spread right or left and assume a laterally convex shape with an angulated scintillating edge. Additional loss or blurring of central vision may occur. Sometimes scotoma without positive phenomena may occur and it enlarges gradually.

Typical aura with migraine headache – diagnostic criteria (ICHD-2):

A. At least 2 attacks fulfilling criteria B-D

B. Aura consisting of at least one of the following, but no motor weakness:

1. fully reversible visual symptoms including positive features (eg, flickering lights, spots or lines) and/or negative features (ie, loss of vision)
2. fully reversible sensory symotoms including positive features (ie, pins and needles) and/or negative features (ie, numbness)
3. fully reversible dysphasic speech disturbance

C. At least two of the following:

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 last ≥5 and ≤60 minutes

D. Headache fulfilling criteria B_D for *1.1 Migraine without aura* begins during the aura or follow aura within 60 minutes

E. Not attributed to another disorder.

In basilar–type migraine visual symptoms occur simultaneously in both temporal and nasal fields on both eyes.

Impairment of consciousness during migraine attacks seems to occur in young patients with basilar-type migraine. The *basilar-type migraine* – first described by Bickerstaff in 1961 – is a type of migraine with aura symptoms clearly originating from the brainstem and/or from both hemispheres simultanously affected, but no motor weakness (ICHD-2).

Basilar-type migraine – diagnostic criteria (ICHD-2):

A. At least 2 attacks fulfilling criteria B-D

B. Aura consisting of at least one of the following fully reversible symptoms, but no motor weakness:

1. dysarthria
2. vertigo
3. tinnitus
4. hypacusia
5. diplopia
6. visual symptoms simultaneously in both temporal and nasal field of both eyes
7. ataxia
8. decreseds level of consciousness
9. simultaneously bilateral paraesthesias

C. At least two of the following:

1. at least one aura symptom develops gradually over ≥ 5 minutes and/or different aura symptoms occur in sucession over ≥ 5 minutes
2. each aura symptom lasts ≥ 5 and ≤ 60 minutes

D. Headache fulfilling criteria B_D for *1.1 Migraine without aura* begins during the aura or follow aura within 60 minutes

F. Not attributed to another disorder.

The most common cause of loss of consciousness in migraine is *syncope*, possibly induced by sever headache.

The association between migraine and epilepsy is complex and bi-directional.

- Typical generalized seizures, and even status epilepticus, may occur during migraine attacks.
- Headache accompanied by visual disturbances, nausea and vomitting may follow generalized seizures.

Migraine-induced epileptic seizures. MIGRALEPSY

Seizures have been reported to occur during or immediately following a migraine aura.

Epileptic seizures are vulnerable to many extrinsic and intrinsic factors, so it could be triggered by the cortical changes induced by migraine. Most of these are occipital seizures imitating migraine aura.

The association between migraine and epilepsy is named "migralepsy". The term **migralepsy** is used to denote epileptic seizures occurring between the migrainous aura and the headache phase of migraine.

A logical succession of events in migralepsy case is as follows: migraine aura → followed by a epileptic seizure triggered by the cortical changes induced by migraine aura → followed by migrainous headache.

Even migraine and epilepsy are very common diseases in neurological practice, only a few case reports of migralepsy have been published. It is difficult to differentiate "migralepsy" from occipital seizures imitating migraine aura and most of reported cases are in fact occipital epilepsy. For exemple, two of the three "migralepsy" patients of Lennox and Lennox (1960) seemed to have symptomatic and idiopathic occipital epilepsy with visual hallucinations. According to Panayiotopoulos none in 1550 cases of "migralepsy" has been confirmed.

These concept of "migralepsy" cannot be denied, but should be used cautiously, after a sharp diagnosis (Panayiotopoulos CP).

Headache attributed to epileptic seizure

According to the International Classification of Headache Disorders. 2nd edition (ICHD-2), there are recognised 2 types of headaches attributed to epileptic seizure:

a) Hemicrania epileptica;

b) Post-ictal headache.

a) Hemicrania epileptica

Synchronous ipsilateral headache with migrainous features occuring as an ictal manifestatinon of the seizure discharge is recognised, albeit rare. Diagnosis requires the simultaneous onset of headache with electroencephalographically-demonstrated ictal discharge.

Hemicrania epileptica – Diagnostic criteria (ICHD-2).:

A. Headache lasting seconds to minutes, with features of migraine, fulfilling criteria C and D

B. The patients is having a partial seizure

C. Headache develops synchronuosly with the seizure and is ipsilateral to the ictal discharge.

D. Headache resolves immediately after the seizure

b) Post-ictal headache

Seizure provoke a syndrome similar to the headache phase of migraine in 50 % of epileptics.

Post-ictal headache with migrainous features is a well-recognised consequence of a seizure discharge. Post-ictal headache is often indistinguishable from migraine headache and associated with nausea and vomiting. It is equally common in those with or without a family history of migraine.

Post-ictal headache – Diagnostic criteria (ICHD-2).:

A. Headache with features of tension-type headache or, in a patient with migraine, of migraine headache and fulfilling criteria C and D

B. The patient has had a partial or generalised epileptic seizure

C. Headache develops within 3 hours following the seizure

D. Headache resolves within 72 hours after the seizure.

Post-ictal headache has been reported in patients with symptomatic epilepsy, but it is mainly emphasised in idiopathic occipital seizures. The seizure discharges in the occipital lobes triggers a migraine headache through trigemicovascular or brainstem mechanisms.

In some patients, post-ictal headache develops in 3-15 minutes after the end of visual hallucinations and it is longer and more severe after visual seizures of longer duration.

EPIDEMIOLOGICAL ASPECTS

Migraine and epilepsy may coexist without being a contributing risk factor for the other.

Comorbidity is used to refer the greater than coincidental association of two conditions in the same individual.

Migraine is comorbid with other neurological and psychiatric disorders, including stroke, epilepsy, depression and anxiety disorders

An altered brain state could increase the risk of both migraine and epilepsy. Genetic or environmental risk factors may increase neuronal excitability or decrease the threshold to both types of attacks.

Migraine and epilepsy may be co-morbid as certain brain disorders (eg, MELAS) predispose patients to both epilepsy and migraine occuring remotely form each other.

A structural brain lesion like an arteriovenous malformation could be the cause of both migraine-like headaches and epileptic seizures.

There appears also to be a high incidence of migraine in certain forms of epilepsy such as benign occipital epilepsy, benign rolandic epilepsy and corticoreticular epilepsy with absence seizures

Epilepsy incidence in migraine suffers

Basser found a significant greater incidence of epilepsy among 1830 migraine sufferers (5,9%) than in 548 patients with tension headache (1,1%), and a greater total incidence of impairment of consciounsness (including syncope) among migraine sufferers.

Andermann and Andermann reported a median epilepsy prevalence of 5,9% (range 1-17%) in migraineurs, wich greatly exceeds the population prevalence of 5,2%.

Migraine incidence in epileptic patiens

Andermann and Andermann – also reported migraine prevalence in epileptics ranges from 8% to 23%.

Ottman and Lipton explored comorbidity of migraine and epilepsy using Columbia University's Epilepsy Family Study. Among the subjects with epilepsy (probants) the prevalence of a migraine history was 24%. Epilepsy increases the relative risk of migraine by 2,4; both in probants and their epileptic relatives.

Migraine risk was the highest in patients with post-traumatic epilepsy (relative risk=4,1), in this case shared environmental risk factots may contribute to their comorbidity.

PHYSIOPATOLOGICAL LINKS

Migraine is a primary **disorder of the brain** (Goadsby), it may be caused by dysfunction of an ion channel in the aminergic brain-stem nuclei that normally modulates sensory inputs and exerts neural influences on cranial vessels. It is a form of neurovascular headache in wich neural events results in the dilatation of blood vessels, wich, in turn, results in pain and further nerve activation.

Important pathophysiological links may exist between migraine and epilepsỹMutations leading to ionopathic dysfunction, are present in migraine and epilepsy, both conditions being considered as **neuronal channelopathies**.

The most severe form of aura is hemiplegia. **Familial hemiplegic migraine (FHM)** is a rare autosomal dominant disorder characterized by episodes of transient hemiparesis followed by headache.

Different FHM types are now recognised to be associated to several gene mutations:

- In FHM (type 1), the CACNA1A gene mutation (localized to the short arm of chromosome 19p13) lead to a modified synthesis of α_1 subunit of the voltage-gated P/Q-type calcium channel (Ophoff et all, Cell, 1996).
- Mutations in the gene ATP1A2 that encodes the α_2 subunit of the Na^+/K^+ pump are associated with FHM (type 2), linked to chromosome 1q23 (De Fusco M et all., Nat Genet., 2003).
- A novel locus for FHM (type 3) was identified on chromosome 2q24, leading to a heterozygous missense mutation (Gln1489Lys) in the neuronal sodium voltage-gated channel gene SCN1A. This have been associated both with epilepsy and FHM3, reinforcing the molecular links between migraine and epilepsy, two common paroxysmal disorders (Dichgans M et all., Lancet 2005)

CORTICAL HIPEREXCITABILITY IN MIGRAINE

Migraine aura is the human homologue of "cortical spreading depression" (CSD) found by Leao on rabbit cortex. *Oligemia* is the reduction in regional cerebral blood flow in response to depressed neuronal function and is still clearly present when the headache starts.

A short phase of hyperemia precedes oligemia that passes across the cortex from oocipital to frontal area, at a slow rate, without respecting the territory of single blood vessels.

The cortical spreading depression and the spreading oligemia are preceded by a front of neuronal hyperactivity illustrataed by abormal epileptiform discharges on EEG (electroencephalography).

The intense neuronal activity is folllowed by efflux of K^+ from nerve cells, the glial cells (astrocits) are involved in the clearance of brain K^+. The human cortex has the lowest ratio of glial to neuronal cells, suggesting a reduced treshold for CSD.

PET (positron emissiontomography) studies (Weiller 1995, Bahra 2001) showed brainstem activation during acute migraine and the persistence of this activation after the headache phase.

The basic biologic problem in migraine is the dysfunction of an ion channel in the aminergic brainstem nuclei that normally modulates sensory input and exerts neural influences on cranial vessels.

Neurophysiological, magnetic resonance spectroscopy, biochemical and epidemiological data suggests that migraineurs have an interictal state of cortical hyperexcitability, characterised by a reduced threshold and increase responses.

The excitability level is proportional to attack frequency. Its physiological basis may be:

- defective mitochondrial oxidative phosphorilation
- low intracellular magnesium
- increased levels of neurotoxic aminoacids
- inherited dysfunction of calcium channels,
- or a combination of these factors.

In migraine patients there is a low level of plasmatic magnesium during the migraine attack comparing to normal subjects, the low magnesiemia is associated with the frequency, severity and duration of the headache. High–dose riboflavin could be a prophylactic antimigraine treatment (J Schoenen).

The physiophatologycal background consist in the presence of cortical hyperexcitability in both diseases with EEG abnormalities between attacks, with a low epileptic and migraine threshold. This threshold is set by genetic factors and rised by prophylaxis and anticonvulsivants

The use of anticonvulsivants (neuromodulators) in migraine prevention is justified by the fact that migraine and epilepsy are both chronic diseases with recurrent attacks of central nervous system (CNS) dysfunction.

Using the mutation R192Q of the gene CACNA1A, Van den Maagdenberg succeded to select a line of genetic modified mice with a great susceptibility for CSD. Starting from the assumption that the depression of cerebral metabolism follows the cerebral hyperexcitability, these animals could be used as model for the study of migraine prophylaxis by modulation of the hyperexcitability.

EEG FINDINGS IN MIGRAINE

Electroencephalography (EEG) is a record of cerebral activity using electrodes placed on the scalp. EEG is a non-invasive and relatively low-cost study and remains one of the major tools for investigation of epilepsy showing a good sensitivity and specificity. It also play a role in the evaluation of other focal and diffuse CNS disorders.

The usefulness of EEG in diagnosis of headache is debated.

IOlder studies showed that the **interictal EEG recorgings** in migraineurs may reveal a variety of nonspecific changes, including focal and generalized sloe-waves and abnormal responses to hyperventilation and photic stimulation. Focal and lateralized spike-wave abnormalities may occur in the absence of a history of epilepsy, but tend to be more common in patients with migraine with aura. Also, abnormalities tend to be more common in younger patients, and in some studiues in association with attack frequency and severity.

Intermittent photic stimulation oftern shows an occipital driving response extending into the range of above 20 flash/sec (“H response”: after Golla and Winter, 1959). Smyth and Winter (1964) considered this response as almost specific for migraine.

In older studies**, ictal EEG** recordings during migraine attacks have shown diffuse or focal slow-wave abnormalities, or no abnormality at all,. Usually epileptic discharges are not sen unless they are present also on the interictal recordings.

According to American Academy of Neurology “EEG is not useful in the routine evaluation of patients with headache (guidline)”. In order to have an accurate differential diagnosis, EEG may be use in headache patients ifvthe bclinical history suggests aseizure disorder (Rosenberg, et al. 1995).

However, ”ictal EEG could be useful in certain patiens suffering from hemiplegic and basilar migraine” (Hughes R, Brainin M, Gilhus NK – European Handbook of Neurological Management, 2006).

THERAPEUTIC ASPECTS

Comorbid conditions may impose therapeutic limitations, but may also create therapeutic opportunities. The anti-migraine, anti-epileptic agents – like sodium valproate and topiramate – may prevent attacks of both migraine and epilepsy.

The positive response of migraine symptoms to anticonvulsants is a circumstantial evidence to support association between migraine and epilepsy. In some cases withdrawal of anticonvulsant resulted in recrudescence of migraine attacks.

Virtuallly all anticonvulsivants (more properly-termed neuronal-stabilizing agents or neuromodulators) have been shown to have efficacy in treating headaches. This may be concordant with the theory that migraine reflect a brain disorder.

Sodium valproate an topiramate are officialy approved by the FDA for the prophylactic treatment of migraine headaches.

Sodium valproate (VPA) facilitates the effects of the inhibitory neutotransmitter gamma-aminobutyric acid (GABA).

Sodium valprotate is an effective preventive medication for migraine at a low dose of 600 mg/

day (500-750 mg/day) (Kaniecki,1997; Klapper, 1997; Silberstein et al., 2000; Freitag et al., 2002).

It is especially useful when migraine occurs with comorbid epilepsy, anxisty disorders or manic-depressive illness. It can be administrated in patients who have copntraindications to beta-blockers (depression, Raynaud's disease, asthma. diabetes).

Side effects include sedation, hair loss, tremor and changes in cognitive performances Heoatotoxicity is the most serious side effects.

Topiramate (TPM) has multiple pharmacological actions involving blockade ofvsodium chaqnnels and high-voltage-activated calcium channels, attenuation of kainite-induced responses and enhancement of GABA-ergic neurotransmission. It also inhibits carbonic anhydrase.

Topiramate in a dose between 25 and 100 mg/day is effective in migraine prevention (Brandes et al, 2004; Diener et al., 2004: Silberstein et al., 2004).

Side effects related to CNS include ataxia, poor concentration, confusion, dysphasia, dizziness, fatigue, paresthesia, somnolence, word-finding difficulties and cognitive slowing. It increase the risk of nephrolithiasis tenfold and should be avoided in patients with history of kidney stones.

Anorexia and weight loss are common in TPM treatment. TPM could be used in migraine prophylaxis in obese patients. Topiramate therapy was well-tolerated and effective in reducing the frequency and severity of migraine in refractory headache patient.

Lamotrigine (LTG) selectively blocks the slow inactivated state of sodium channel, thereby preventing the release of excitatory amino-acid neurotransmitters, particularly glutamate and aspartate. Lamotrigine is used in migraine with aura. Lamotrigine did not reduce the frequency of migraine attacks but is probably effective in reducing the frequency of migraine auras (Steiner et al., 1997; Lampl et al,. 1999). Side effects of TLG includes nausea, insomnia, vomiting, dizziness, diplopie, ataxia, tremor. Rash could appear in the treatment initiation, so gradual introduction of LTG reduce the likehood of rash.

Gabapentin (GBP) acts by binding to the α2-δ subunit of the neuronal voltage-gated calcium channels, inhibiting calcium flow and neurotransmitter release from presynaptic neurons. Gbapentin showed a significant efficacy in one placebo-controlled trial in doses between 1200 and 1600 mg (Mathew et al., 2001). Side effects of GBP are mild and transient (drowsiness, ataxia, dizziness and nystagmus).

CONCLUSIONS

Epilepsy occuring during migraine attack is uncommon and, in most cases, simly reflects a low seizure threshold, with the migraine attack acting as a trigger for the seizures. However, such development alaways suggest the posibility of underlying structural abnormality and should be investigated accordingly.

It is possible that migraine could be a factor in secondary epilpeptogenesis, particulary in young patients with frequent, severe attacks.

Recent basic research findings revealed possible pathophysiological links between migraine and epilepsy.

Anticonsulsants may be useful in migraine prophylaxis, especiallly in patients who are resistant to standard anti-migraine drugs.

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