

The migraine-epilepsy syndrome

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EL SINDROME MIGRAÑA-EPILEPSIA

RESUMEN

La migraña y la epilepsia tienen varios puntos en común sintomática clínica y genéticamente lo que ha sido postulado por más de cien años. El fenómeno referido como migraña-epilepsia sugiere que exista una patofisiología común. El síndrome de migraña o epilepsia tiene fenómenos comunes de dolor abdominal, jaqueca, anomalías del EEG y respuesta a drogas antiepilépticas. En ocasiones el paciente puede tener un ataque migrañoso o una convulsión o en otras ambas. La comorbilidad puede explicarse por estados de hiperexcitabilidad neural. Alteraciones electroencefalográficas son comunes en estos estados. En apariencia el glutamato tiene un papel importante tanto en la migraña como en la epilepsia. Según el lóbulo afectado los síntomas prematorios pueden variar de alteraciones visuales a gástricas, por lo que no deben usarse divisiones artificiales.

Palabras clave: migraña, epilepsia, alteraciones comunes, electroencefalograma.

ABSTRACT

Migraine and epilepsy have common points from the clinic symptomatic and genetic view and this has been noticed for more than hundred years. The migraine epileptic syndrome suggests a common pathophysiology with symptoms as abdominal pain, headache abnormalities at the spinal fluid and good response to antiepileptic drugs. Some times the patient might have both symptoms headache and convulsions and both

represent a neural excitation. Since that the glutamate has an important role in both pathologies depending on the part of the brain more affected the symptoms might vary from visual to abdominal phenomena.

Key words: migraine epilepsy, EEG abnormalities, glutamate, diagnosis.

The first steps of a practical approach by physicians in recognizing and treating neurologic diseases are to recognize that there are various overlaps between migraine and epilepsy. Epileptic seizures and classic migraine episodes may occur in the same patient. Migraine and epilepsy share several genetic, clinical, evolutive and neurophysiologic features. A relationship between epilepsy and migraine has been postulated for over a hundred years and the syndrome of Migraine-Epilepsy illustrates this complex relationship between both.

Clinically, the diagnosis of epilepsy is supported by additional positive motor phenomena or by a transition into a complex partial seizure, e.g. when epileptic activity secondarily spreads into a temporal lobe. Secondarily generalized seizures, however, may also occur in patients with migraine. The complex relationship between migraine and epilepsy is highlighted by the occurrence of a seizure during a migraine attack without aura. This phenomenon,

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referred to as “Migralepsy”, suggests an inherent overlap in the underlying pathophysiology of these events¹⁷.

A general pathogenetic model of migraine and seizures may be characterized by a given predisposition, various co-factors which enhance the tendency, and finally, trigger mechanisms, which induce an attack. In assessing the importance of various factors thought to be related to idiopathic migraine-epilepsy syndrome, it is necessary to differentiate between causal relation, unspecific association, and coincidence.

The syndrome of migraine-epilepsy is infrequent phenomena with paroxysmic episodes of headache or abdominal pain, awareness, EEG abnormalities and positive results with the introduction of antiepileptic drugs. The most constant characteristic is the paroxysmal occurrence of the symptoms, frequently triggered by emotional stress, fatigue or flashing light, heralded by prodromal signs and symptoms such as pallor, flushing, sweating, languor, irritability and dizziness and on occasions sensory disturbances or transient hemiparesis, followed by sleep. A individual may have a seizure on one occasion and a classic attack of migraine on another. Histories of children with epilepsy occasionally disclose that the seizures have been preceded for several years by attacks of migraine. However, epilepsy is more likely to become migraine than migraine to become epilepsy. A familial history of the syndrome is present in 70 to 85 per cent of children with migraine and in 3 to 8 per cent of those with epilepsy. The history of migraine is more common in the families of epileptic patients than in the normal population.

The syndrome has been elaborated with bases in his clinical features and in the EEG contributions and long-term video/EEG that has allowed improved differentiation between epileptic syndromes and non-epileptic disorders that may mimic epilepsy clinically or migraine disorders; recognition of its relatively benign course may prevent unnecessary investigation and undue alarm.

A critical review of the data indicative of a relationship between migraine and epilepsy show that the pathogenesis point towards their combined occurrence are frequent. These data are considered under five major headings: genetic, epidemiological, clinical, electroneurophysiological and neurochemical.

Besides purely coincidental combinations, a variety of reasons is held responsible for this side-by-side occurrence.

The relation of migraine and epilepsy

The two conditions were thought to be closely related by Liveing and Vining, while others held that the occurrence of migraine and epilepsy in the same patient is probably coincidental, for example Bramwell, Alvarez and Brain. In discussing the relation of migraine and epilepsy, Gowers in 1907, began with alteration where “one replaces the other in the same subject” but also observed that epileptic attack and paroxysmal headaches may coexist.

Dealing with the premonitory symptoms of migraine and their distinction from epilepsy, he emphasized the difference in duration and also pointed out that when isolated prodromas occur, they are often very much briefer than when followed by headache and might easily be thought to be “minor epileptic seizures” but the identity of character with those that preceded the headaches made their nature certain.

Risk for migraine and epilepsy

In adults, Marks and Ehrenberg studied the relationship between migraine and epilepsy in 395 seizure patients, 20% also had migraine syndrome and 3% of these patients experienced seizures during or immediately following a migraine aura. Patients with catamenial epilepsy and patients with migraine with aura were at an increased risk for an association between these two disorders.

Lees and Watkins found only 2.1 per cent of illeir cases of migraine showed features of epilepsy, and Lance and Anthony found the same incidence of epilepsy, 2 per cent, both in their series of migraine and tension headaches. Ely in 1930, from the ancestral histories, concluded that “migraine is possibly the morbid ancestor of both migraine and epilepsy”.

Classical investigations have shown that epilepsy occurs more commonly in patients with migraine that would be expected by chance (Slatter 1968, Hockaday and Whitty 1969) although the frequency of the association varies from study to study. By the other hand, the incidence of migraine studied in several groups of patients show that migraines were present in 62% of the patients with centro-temporal epilepsy, 34% of the patients with absence of epilepsy, 8% of the patients with partial epilepsy and 6% of the patients with cranial trauma. These results suggest that the association of centro-temporal epilepsy and migraine is non-fortuitous as well as, to a lesser degree, absence of epilepsy and migraine and that centro-temporal epilepsy together might be a feature for the diagnosis of migraine.

Migraine in childhood and adolescence seems to be definitively associated with vegetative dysfunction, abdominal symptoms and hormonal factors and possibly with allergic reactions, whereas a relation to epilepsy can be excluded.

Pathogenic models of the syndrome of migraine-epilepsy

Electroencephalographic abnormalities

The comorbidity of migraine and epilepsy may be explained by a state of neuronal hyperexcitability that increases the risk of both disorders. Individuals with epilepsy are 2.4 times more likely to develop migraine than their relatives without epilepsy. Risk of migraine is elevated in patients with partial-onset and generalized-onset seizures. There are rare seizures, either focal or generalized, usually followed a migrainous aura that seemed to be readily controlled with anticonvulsant medication. Whether the syndrome is migrainous or epileptic has yet to be elucidated.

Electroencephalographic abnormalities are seen in 50 to 70 per cent of children with migraine and 80 to 90 per cent of those with epilepsy as compared to 15 to 20 per cent in the normal population. A positive spike pattern of 14 and 6 cycles per second was demonstrated by Whitehouse and his co-workers in 46 per cent of children with migraine as compared to 18 per cent in normal controls. Chao, *et al* find that 50 per cent of children with convulsive-equivalent epilepsy also has this spike abnormality in their electroencephalograms. This EEG pattern disturbance is the primary factor in migraine, vascular and humoral factors being secondary manifestations.

Electroencephalographic abnormalities with temporo-parieto occipital or temporo-occipital spikes or spike-wave complexes suppressed by eye opening show different neurological syndromes: migraine with aura, vertebrobasilar migraine, visual phenomena, epilepsy, psychomotor retardation and syndrome of migraine-epilepsy. All of the EEG finding of occipital spike-wave complexes seems to extend to different neurological syndromes.

The high incidence of EEG abnormalities was first noted in patients with migraine by Dow and Whitty and subsequently by Selby and lance, Lees and Watkins, Barolin, Otero, *et al* and Townsend, the latter questioning their diagnostic importance. Ziegler and Wong found a high percentage of paroxysmal disorders in children with migraine and to a less extent in their siblings. Smyth and Winter described a photic driving response to high frequencies in patients with migraine, and Towle found the most significant thing

was an exaggerated and prolonged response to hyperventilation. Slatter concluded that the response to photic stimulation reflected a constitutional predisposition to migraine and suggested that permanent cerebral damage resulting from migraine may produce abnormal electroencephalographic findings and rarely cause local epileptic changes. This suggestion is very difficult to substantiate simply based on a temporal sequence of events in successive electroencephalograms. The generally dysrhythmic electroencephalograms of some migraine patients could not be distinguished from certain of the epilepsies and that the aura in migraine is associated with cortical firing, differing only in degree but not in kind from other paroxysmal cortical discharges.

Spreading depression of activity of the cerebral cortex

The higher speed of trans-synaptic propagation of epileptic discharges and postictal inactivation causes a more rapid time-course of the epileptic "aura" as compared to a migraine aura resulting from a "depolarization spreading" by diffusion. Records of the entire sequence from migraine aura to partial seizure show distinctive changes on the EEG during the migraine aura that preceded the onset of an electrographic complex partial seizure.

Leao's first paper on "Spreading Depression of Activity of the Cerebral Cortex" appeared in 1944. The study originated in an attempt to secure more data for the understanding of the electrocorticogram which occurs in "experimental epilepsy" and of the conditions in which it is brought forth by electrical stimulation. Early in the development of the study, an interesting response elicited by electrical stimulation was noticed in the cortex of rabbits. The distinctive feature of this response was a marked enduring reduction of the "spontaneous" electrical activity of the cortex. The "depression" slowly spread in all directions, successively affecting adjacent areas.

Spontaneous activity at the stimulated region was often well recovered at a time when the depression was just starting in distant parts. Specific activity different from the spontaneous often developed during the period of depression of a region. The most common type of this activity was composed of large slow localized potential waves during which one electrode became negative with respect to others 1-3 mm. distant. Fast components might also appear and the activity, when intense, closely resembled the "seizure pattern" of experimental epilepsy. Milner noted correspondence between the scotomas of migraine and the spreading depression of Leao. He drew his

evidence from Lashley's paper from 1941, on patterns of cerebral integration indicated by scotomas of migraine.

Interictal and ictal EEG recordings can be important to prove an epileptic origin, but their sensitivity is low if ictal discharges remain limited to a small brain area. In rare cases, measurements of ictal cerebral perfusion can contribute to the differential diagnosis.

There is a possible connection between scotoma in migraine and epileptic discharge. It is proposed that spreading depression, as the basis of the migraine prodromata, is preceded by a moment of intense neuronal excitation which change the epileptic intercritical activity into a critical one¹⁰. In some cases the EEG show an epileptogenic occipito-temporal focus that correspond to the region of the scotoma origin.

Glutamate metabolic actions in neuronal excitatory modulation

It has become increasingly apparent that glutamate occupies a central position in the development of epilepsy or in the onset of a migraine incident. The importance of glutamate is explained by a variety of functions in the CNS: as a dominant constituent of many proteins, by its intermediary role in linking energy metabolism to that of many other amino acids, and as the virtually exclusive precursor of GABA.

Moreover, glutamate serves as the primary substrate in ammonia detoxification and the product, glutamine, actively participates in CSF water homeostasis.

Glutamate occupies by its direct electrophysiological and metabolic actions on neurons and glia, via at least four distinct types of receptor proteins, and is implicated in a number of critical mechanisms of information. These include neuronal excitatory modulation, intracellular Ca²⁺ redistribution, and key metabolic (phosphorylation) mechanisms. The phenomena, when exaggerated due to excessive extracellular glutamate levels, may cause pathological effects such as hypersynchrony-epilepsy, Spreading Depression- Migraine, high internal Ca (2+)-damage, impaired phosphorylation/dephosphorylation-necrosis, among others. Not surprising therefore that severe epilepsy may eventually cause CNS cytoarchitectural and metabolic damage, or conversely, that neural tissue trauma not infrequently gives rise to epilepsy many years later. Both conditions are associated with a persistent, excessive leakage or release of glutamate

into the extracellular milieu. An electrophysiological and neurochemical commonality between migraine and epilepsy has also been noted.

Mg (2+) deficiencies and disordered energy metabolism

It is hypothesized that disturbances in magnesium ion homeostasis may contribute to brain cortex hyperexcitability and the pathogenesis of migraine syndromes associated with neurologic symptoms.

Studies by multiplexed spectroscopic imaging of patients with migraine with a neurologic aura have suggested that disordered energy metabolism or Mg (2+) deficiencies may be responsible for hyperexcitability of neuronal tissue in migraine patients. When these studies are extended to include multiple brain regions and larger numbers of patients those disordered energy metabolism or Mg (2+) deficiencies has a tendency to be significantly lower in the posterior brain regions. In contrast, migraine patients without a neurologic aura may exhibit compensatory changes in [Mg (2+)] and membrane phospholipids that counteract cortical excitability. Cerebral blood flow measured by radionuclide tracing in migraine-free interval tend to speeding up. By disintegration of cerebrovascular regulation and vascular supply of the neuron, migraine may promote secondary epileptogenesis.

Distinguishing epileptic events from nonepileptic not be paroxysmal neurologic events represents a common diagnostic challenge. Studies carried out on large population samples have shown that the relationships between migraine and epilepsy may be of the following type:

1. Associated attacks, with migraine and seizures occurring quite independently of one another;
2. Combined attacks, with the two types of attacks succeeding one another in time;
3. Basilar artery migraine with seizures and marked EEG abnormalities;
4. Benign epilepsies with occipital discharges end
5. Migraine and intercalated seizures.

There is an increasing body of evidence to suggest that benign rolandic epilepsy and benign occipital epilepsy of childhood are frequently associated with migraine, two conditions which probably have different pathophysiology, although to be related to idiopathic migraine-epilepsy syndrome.

A detailed analysis of the aura does provide sufficient information for classifying the disorder as an aura in migraine or as a simple partial epileptic seizure in most cases. Visual phenomena as if lightnings, disturbed contours of objects, or skotoma, can be due

to ophthalmological diseases, but can also occur as symptoms generated by the central nervous system ("aura") in migraine or epilepsy. A subsequent hemicrania is considered as a hallmark of migraine, but in many cases does not allow for a certain distinction from postictal headaches in patients with focal epilepsy.

Misdiagnosis of visual seizures as visual aura of migraine is common; but the analysis of differential diagnosis between migraine and the occipital epilepsies conclude that elementary visual hallucinations, blindness or both, alone or followed by headache and vomiting of symptomatic occipital epilepsy are identical to those of idiopathic occipital epilepsy. Progress to temporal lobe structures is different and consistent with symptomatic occipital lobe epilepsy. The clinical diagnosis of visual seizures is easy if individual elements of duration, colour, shape, size, location, movement, speed of development and progress are identified. They are markedly different from visual aura of migraine, although they often trigger migrainous headache, probably by activating trigemino vascular or brain stem mechanisms.

Benign occipital epilepsy of childhood is an idiopathic partial epilepsy syndrome with elementary visual symptomatology, frequently associated with other ictal phenomena. Seizures are usually followed by postictal headache and are often associated with interictal occipital rhythmic paroxysmal EEG activity that appears only after eye closure. It has been defined by Panayiotopoulos as consisting of brief, infrequent attacks or prolonged status epilepticus and characterized by ictal deviation of the eyes and/or head and vomiting, occurring in children usually between the ages of 3 and 7 years.

Migraine and benign focal spikes of childhood (BFSDC) may be genetically linked. In migraine with BFSDC, frequently interictal EEGs records are interpreted 89% normal and 9% with benign focal epileptiform discharges (BFEDC), independent of history. Other EEGs records have temporal spikes, and few have background slowing. The patients with BFEDC did not differ from others with migraine. None has epilepsy. This incidence of 9% is higher (p less than 0.0001) than the incidence of BFEDC in the normal population (1.9%). The significance of this finding is not clear, but migraine and benign focal epilepsy of childhood may be genetically linked, or the vascular abnormality of migraine may cause brain injury to produce sharp waves of low epileptogenicity. Those do not suggest that headaches are epileptic. Patients with occipital

epileptiform abnormalities present with ictal vomiting are often diagnosed as having "Vague Migraine-Epilepsy Syndromes". By the other hand, Parietal and occipital seizures have been investigated relatively little. The most prominent clinical manifestations of parietal epilepsy are elementary sensory phenomena at the beginning of seizures and elementary visual hallucinations in occipital epilepsy. Because of these controversial symptoms, diagnostic criteria may be difficult to define. The wide difference in clinical and EEG manifestations between reported series of parietal and occipital epilepsy also reflects a considerable problem with patient sampling. Classification of epilepsy according to the anatomic division of the brain may be arbitrary, and it may be appropriate to define epileptic syndromes such as sensorimotor seizures or occipito-temporal seizures that cross such artificial divides.

From the existing literature, we can conclude that precise incidence and prevalence of the epileptic syndromes such as sensorimotor seizures or occipito-temporal seizures are largely unknown. A recent community-based study of 252 subjects with partial epileptic seizures in an epileptic population of 594 showed that parietal seizures and seizures of posterior origin each comprised 6.3% and central or sensory-motor seizures comprised 32.5% of focal seizures in the 160 cases in which seizures could be sub classified (Manford, *et al*, 1992). This incidence seems low for occipital seizures as compared with the 1953 study by Gibbs and Gibbs, who observed occipital epileptiform activity in 8% of subjects with focal epilepsy.

The benign childhood epilepsy with occipital paroxysms (BCEOP) with early onset has a benign course despite of initial attacks of partial status epilepticus and/or migraine attacks. Since occipital seizures differ depending on age, an age-dependent epilepsy with occipital paroxysms exists; a preferential age for the association between epilepsy and basilar migraine also exists.

In all of benign childhood epilepsy with occipital paroxysms, photic stimulation induce seizures in the right occipital lobe followed by clinical and EEG signs suggesting infra-sylvian spreading to ipsilateral mesiotemporal limbic structures and by vomiting, appearing at late stages of the attacks. Seizure spread is very slow last 16 and 25 minutes. Vomit can be a late ictal phenomenon resulting from temporal lobe spread of seizures originating in the occipital lobe. Scalp EEG is frequently negative or maybe misleading. Hence, role played by maturational processes in these

various aspects of epilepsy, migraine and occipital seizures in children is important; furthermore, spread of epileptic discharges from the parietal and occipital lobes to frontal and temporal regions may obscure seizure origin.

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