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Hypothesis on neurophysiopathological mechanisms linking epilepsy and headache ☆

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Summary The comorbidity between epilepsy and migraine has been well known for a century, yet it is still not fully understood; the two disorders also share some risk factors, symptoms, and preventive drug therapy. A series of clinical observations and scientific data support the hypothesis of alteration of cortical excitability as a possible mechanism underlying their pathology, with both disorders characterized by transient paroxysmal neurological disturbance. So far, the numerous pathophysiological mechanisms responsible for neuronal hyperexcitability have only been studied in familial hemiplegic migraine (FHM), but they do suggest a link between migraine and epilepsy. Several studies support the hypothesis of a clinical continuum between some types of migraine and some types of epilepsies, with possibly even a complete overlap, representing, in particular cases, headache as the sole ictal manifestation of seizures. Taking into account the data in the literature, we hypothesize that several aetiopathological noxae (either environmental or genetics), such as Na+–K+ ATPase pump impairment, converging on a common final pathway represented by neuronal membrane hyperexcitability, could manifest as either epilepsy or headache/migraine, or both.

The potential implications arising from this point of view include (a) a revision of headache/migraine diagnostic criteria as the sole ictal epileptic manifestation in international classifications of both epilepsies and headache disorders; (b) the careful follow-up of patients with headache/migraine as a residual feature, taking into consideration a revised concept of ''complete seizure control'' to avoid mistakes due to inopportune withdrawal of antiepileptic treatment.

In addition, we suggest that headache is associated with other ictal-sensitive and motor features (more than those reported); these may be highly underestimated due to impairment of consciousness during complex partial seizures with or without secondary generalization.

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Introduction

Migraine and epilepsy are both disorders with recurrent and paroxysmal manifestations of disturbed brain function; they can precede or follow each other, or occur simultaneously. Despite our increasing knowledge, so far, most authors think that the definitive differential diagnosis of either epilepsy or migraine should still be based mainly on a clinical judgment in every case. Although, in most cases, this is probably true, we nonetheless think that we may soon be able to demonstrate that these disorders represent two aspects of the same neurophysiopathological phenomena.

Firstly, we have to consider the neural cell excitability as a physiological condition whose transient and fluctuant characteristics are indispensable for normal neurological functioning. In fact, the excitability of brain cells represents the essential age-related properties of nervous tissue without which our normal nervous system would not be able to function. These neurophysiologic characteristics are modified quantitatively and topographically by age. Secondly, we know that this physiological ''double-edged sword'' may sometimes be responsible (due to an increase in cortical excitability) for various epileptic conditions, such as rolandic epilepsy or other childhood forms of benign idiopathic partial epilepsy. These have recently been included in the concept of a ''Benign Childhood Seizures Susceptibility Syndrome'' [1—3], which represents, in fact, a constitutional, topographically age-related, multifocal, cortical hyperexcitability.

This neurophysiological point of view provides a better understanding of the link between epilepsy and migraine as conditions caused by the same altered cortical excitability. This may sometimes result in a complete overlap, with headache as the sole manifestation of epileptic seizures [4,5]. Recent clinical [4—6] and genetic [6,7] studies have reported an association between migraine/headache and epilepsy, raising the possibility of a common monogenic defect in both occipital lobe epilepsy and migraine with aura [7]. We recently described a 14-year-old girl who had a photosensitive occipital epileptic seizure followed by a status migrainosus that lasted for three days [5]. An EEG revealed an occipital status epilepticus during her migraine attack, and intravenous administration of diazepam, under continuous EEG recording, suppressed both the epileptiform discharges and headache complaints.

Possible common neurophysiological mechanisms

As far as the possible common mechanism(s) that could lead to epilepsy and/or headache/migraine are concerned, we would like to share some reflections on the literature data which might contribute to clarifying the neurophysiopathological link between them.

A recent paper [8] stated that ''...cortical spreading depression (CSD) is probably the most primary event in trigeminovascular system activation in migraine with aura (MA) and perhaps also in migraine without aura (MoA)''. An interictal cortical hyperexcitability could predispose the brain to developing episodes of CSD in MA patients and probably also in MoA affected ones. In fact, it is quite possible that CSD does occur in MoA, but in a cortical region that remains clinically silent with passage of the CSD wave [9]. Taking these considerations into account and working on an experimental animal model, Moskowitz et al. [10] have recently reported that long-term daily administration of migraine prophylactic drugs, including anticonvulsants such as topiramate and valproate, is able to suppress the CSD frequency by 40—80% in a dose-dependent manner compared to a control group.

As stated above, to develop headache/migraine, the subcortical trigeminovascular system responsible for the pain phase has to be activated. It is easy to see that to interfere (for therapeutic effect) with this complex polysynaptic and polymolecular cascade, we must act at several cortical and subcortical levels. So far, the drugs available do not have these properties, which is probably reflected in the limited pharmacological control from anticonvulsant therapy during attacks in headache patients compared to epileptic ones. When headache/migraine represents an epileptic manifestation, as recently documented [4,5], the CSD onset and trigeminovascular system activation can be the result of focal cortical discharge. These discharges, which would be able to cause CSD onset and consequent trigeminovascular activation, may come from different cortical areas; in other words, there is no topographic correlation between a specific cortical area and the onset of headache/migraine, although the occipital area and photosensitivity phenomena often seem to be involved. It remains unclear why epileptic discharges arising from the occipital lobe are more frequently associated with autonomic manifestations. There may have been some selective advantages during human evolution, or maybe the occipital cortex can simply