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R. De Simone • A. Ranieri • E. Marano • L. Beneduce • P. Ripa • L. Bilo • R. Meo • V. Bonavita

Migraine and epilepsy: clinical and pathophysiological relations

Abstract Migraine and epilepsy are both chronic disorders characterised by recurrent neurological attacks, with a partial clinical and therapeutic overlap and frequently occurring together. Although still incompletely clarified, the possible existence of a link between migraine and epilepsy has long been debated. In this paper the epidemiologic evidence of migraine and epilepsy comorbidity, the possible occurrence of both disturbances in close temporal association, possible shared physiopathologic mechanisms and the rationale for antiepileptic drug use in migraine prophylaxis will be discussed.

Key words Migraine • Epilepsy • Clinical relations • Pathophysiological relations • Review

R. De Simone (✉) • A. Ranieri • E. Marano • L. Beneduce
P. Ripa • V. Bonavita
Headache Centre, Neurological Sciences Department
University "Federico II" of Naples
Via Pansini 5, I-80131 Naples, Italy
e-mail: rodesimo@unina.it

L. Bilo
Epilepsy Centre, Neurological Sciences Department
University "Federico II" of Naples
Naples, Italy

R. Meo
Neurology Outpatients Service
Azienda Sanitaria Locale 1
Naples, Italy

V. Bonavita
Istituto di Diagnosi e Cura Hermitage Capodimonte
Naples, Italy

Background

Migraine and epilepsy are among the commonest neurological diseases observed in outpatient neurological settings. Although still incompletely clarified, the possible existence of a link between migraine and epilepsy has long been debated [1]. Both disorders are characterised by recurrent neurological attacks with a partial clinical and therapeutic overlap. A number of symptoms, including post-event lethargy, impaired or loss of consciousness, visual disturbances, visual and hormonal triggering factors, vertigo, paraesthesias, hemiparesis and aphasia, can be commonly observed in both conditions [2]. Moreover there is evidence of an epidemiological association between these two conditions. Besides similarities, a number of substantial differences between migraine and epilepsy are to be highlighted. The prevalence of idiopathic forms is much more frequent in migraine than in epilepsy; the definite female prevalence reported in migraine is not evident in epilepsy [3]. Migraine prevalence is low during childhood, peaks in adult age, above all in women, and decreases in old age; on the contrary, epilepsy incidence is highest in extremes of life [4]. In both diseases, monogenic forms are infrequent, but a familial transmission has been found more frequently in migraine. Finally, because the consequences of even occasional seizures are more health-threatening than those of migraine, the traditional goal of epilepsy treatment is the complete control of seizures whereas migraine treatment may be tailored to the reduction of disability within satisfactory limits.

Migraine/epilepsy comorbidity

The prevalence of epilepsy ranges between 0.5% and 1.0% in men and women [4]; the overall prevalence of migraine is about 12% (15%–17% in women and about 6% in men) [5]; the occurrence of both disorders in the same individual only

by chance is therefore expected in about 1% of migraineurs and 12% of epileptic subjects. Available literature data suggest that migraine and epilepsy are linked by a definite *comorbidity*, i.e., they can be observed in the same individual more frequently than expected on the basis of coincidental association. One of the first studies in this field indicates that the prevalence of epilepsy in persons with migraine ranges from 1% to 17% with a median of 5.9%, substantially higher than the population prevalence of epilepsy [6]. On the other side, the reported frequency of migraine in epileptic populations ranges from 8.4% to 23.0% [7]. Although other studies confirm this association, indicating that the risk of migraine is more than twice as high in persons with epilepsy than in persons without epilepsy [8], at least two recent clinical investigations suggest that headache is not encountered more frequently in patients with epilepsy than in the normal population [9, 10]. The discordance of findings may be referred to variation in the definitions of migraine used in the different studies and also, in several studies, to the absence of controls. Another problem is that most of the available studies are from secondary or tertiary care settings: as co-occurrence of diseases increases the probability for medical help seeking, comorbidity may result in grossly overestimation in outpatient clinical series and its evaluation needs to be confirmed in community studies [11]. In a recent study examining comorbidity in an unselected cohort of patients the association between migraine and epilepsy was not identified, suggesting that it could not be encountered in an unselected population [10]. However, this cross-sectional study used morbidity data recorded by general practitioners that could have underdiagnosed migraine.

Remarkably, a strong association between migraine with aura (MWA) and epilepsy has been recently suggested. In a recent study the distribution of seizures across the various types of headache patients showed a strong prevalence in MWA (30.4%) with respect to the other forms of primary headaches [12]. Another population-based case-control study found that the risk for unprovoked seizures was increased in children with MWA and not in patients with migraine without aura [13]. Moreover, the frequency of MWA was found to be significantly higher in patients with comorbidity (41.0%) as compared to the patients with migraine alone (25.8%) [14].

Although large population-based studies are needed to confirm the overall association between migraine and epilepsy, the existence of a definite comorbidity can hardly be denied, at least in MWA patients.

Mechanisms of comorbidity

Mechanisms underlying the epidemiological association between migraine and epilepsy remain uncertain. The three main possibilities are: (1) migraine is a risk factor for epilepsy (for example, by causing cerebral ischaemia and injury); (2) epilepsy is a risk factor for migraine (possibly, by trigeminovascular system activation); and (3) migraine and epilepsy share a pathogenic factor, either acquired or on a genetic basis, leading to a reciprocal risk factor effect. According to the first hypothesis we would expect the incidence of migraine to be elevated before, but not after, the onset of epilepsy. The second hypothesis leads us to expect an excess risk of migraine after, but not before, the onset of epilepsy. The data from a pivotal association study [8] showed that there is an excess risk of migraine both before and after seizure onset, leading to the rejection of both unidirectional casual models and supporting a *bidirectional* comorbidity that reliably suggests the existence of shared pathogenic mechanisms between the two conditions. Ottman and Lipton tested the hypothesis that shared genetic risk factors might account for comorbidity but the analysis failed to confirm this hypothesis because migraine was no more likely in individuals with familial epilepsy than in those without familiality [15]. The authors proposed that the increased cortical excitability that characterises both the diseases might represent the common pathogenic step that can explain the bidirectional comorbidity.

Clinical presentations of migraine/epilepsy comorbidity

In most patients suffering from both migraine and epilepsy the attacks present without a strict chronological correlation, thus reflecting a pure epidemiological comorbidity. Nonetheless, migraine and epilepsy may occur in close temporal relation and a headache attack may precede, accompany or follow an epileptic attack.

Migraine and epilepsy occurring in close temporal relation

Chapter 7 of the International Classification of Headache Disorders – II (ICHD-II) [16] validates "7.6.1 Hemicrania epileptica" and "7.6.2 Post-ictal headache" as headaches *attributed* to epileptic seizures and provides specific sets of diagnostic criteria. A third possible simultaneous presentation of both disorders, limited to MWA patients, refers to the occurrence of a seizure during a typical migrainous aura, an infrequent condition also known as "migralepsy"; the ICHD-II codes this form as "1.5.5 Migraine-triggered seizures" and classify it among the migraine complications; diagnostic criteria require that a seizure, regardless of which type, occurs during or within 1 h after a typical migraine aura.

Although not present in the ICHD-II, cases of a pre-ictal headache (PIHA) not related to a migrainous aura are described. This condition has only rarely been reported [17–19]. In a study on 100 consecutive patients with phar-

macologically refractory partial epilepsy, 11 of them reported PIHA: 7 had early PIHA (within 30 min before seizure onset) and 4 had prodromic PIHA (24 h to 30 min before seizure onset). PIHA was ipsilateral to the seizure focus in all but one and had migrainous characteristics in four [20].

Hemicrania epileptica

Hemicrania epileptica (7.6.1) is a rather uncommon condition; according to ICDH-II criteria it can be diagnosed when a migrainous headache lasting seconds to minutes occurs during the ictal phase of a partial seizure, ipsilaterally to the epileptic discharge. Thus the diagnosis requires an electroencephalographic demonstration of both the synchronicity and the ipsilaterality of manifestations. In a series, only 3 out of 135 (2.2%) epileptic patients had an ictal headache; reported duration of pain ranged between 30 and 60 s [9].

Post-ictal headache (PIH)

Post-ictal headache (PIH) (7.6.2) is a consequence of a seizure discharge that can be frequently observed in occipital lobe seizures but can complicate either partial or generalised seizures. It may present with tension-type features but can be indistinguishable from a true migraine, especially in migrainous patients. ICDH-II criteria for PIH require the onset of pain within 3 h after a seizure and its resolution within 72 h. As many as 50% of epileptic patients complain of a post-ictal headache [17, 18, 21, 22] although prevalence may vary in function of epilepsy type with a higher prevalence in localisation-related occipital lobe epilepsy (OLE). In a study [23] PIH occurred in 41% of temporal lobe epilepsy (TLE) patients, 40% of frontal lobe epilepsy (FLE) patients and 59% of OLE patients. In a series of epileptic patients, migrainous features were found in 26% of subjects reporting post-ictal headache (10% of the total study population). Distribution according to epilepsy type showed a significantly higher prevalence of migraine-like PIH in OLE and TLE than in FLE. Interestingly, a history of migraine does not predict the occurrence of PIH although the incidence of interictal migraine is significantly higher in patients with migraine-like PIH [24] and responsiveness to sumatriptan has been anecdotally reported in PIH [25]. These observations suggest that PIH is a part of epileptic manifestations as its incidence is not affected by a previous history of migraine. Nonetheless, susceptibility to migraine may be predictive of a migraine-like PIH.

Migraine-triggered seizures (migralepsy) (1.5.5)

In a minority of MWA patients an epileptic attack may be precipitated by an otherwise typical visual aura. Although included in the ICDH-II classification, the nosography of migralepsy is still a matter of debate. Although cortical changes induced by the aura phase of migraine may account for the triggering of an epileptic attack in predisposed subjects, migralepsy is observed more rarely than expected considering the high comorbidity rates of migraine and epilepsy. In a series of 412 epileptic patients, migraine-triggered seizures were found in only 1.7% of cases [26], while other series report up to 16% [7]. In addition, the elementary visual hallucinations that precede pain onset in idiopathic or symptomatic occipital seizures may represent the only ictal symptom in such patients, thus mimicking a typical aura migraine. Actually, idiopathic OLE with post-ictal pain is frequently misdiagnosed as MWA, or as *migralepsy* when a progression to extraoccipital manifestations or convulsions do occur [27]. Many features of occipital ictal hallucinations help in its diagnostic differentiation from migraine visual aura. These include [28]:

– an usual duration of less then 30 s that rarely can reach 1 min and only exceptionally can last more than 3 min as opposed to the 5–60 min of a typical aura;
– the perception of multiple small circular spots, almost always bright coloured, appearing in a temporal hemifield and moving horizontally towards the opposite side while increasing in size, a pattern very different from the "fortification spectrum" or the "scintillating scotoma", slowly spreading from point of fixation to one hemifield and leaving variable degrees of blindness in its wake that characterise a visual aura;
– the daily frequency often reported for attacks in idiopathic occipital epilepsy as opposed to a few per year to a few per month frequency commonly observed in migraine aura patients.

Symptomatic co-occurrence of migraine and epilepsy

Finally, the bleeding of an intracranial vascular malformation, either spontaneous or post-traumatic, severe head traumas, and the rare "mitochondrial myopathy with encephalopathy, lactic acidosis and stroke syndrome" (MELAS) may present with simultaneous occurrence of migraine and epilepsy.

Independent occurrence of migraine and epilepsy

Despite the reciprocal influences, migraine and epilepsy occur independently in most comorbid cases. Studies on the clinical characteristics of patients with migraine and epilepsy fail to reveal a specific epileptic profile in subjects with migraine comorbidity. On the contrary, a severe pain, the aggravation by routine physical activity, the presence of photo and phonophobia, and the presence of aura were more frequent in migrainous patients with epileptic comorbidity than in those without [14]. These findings further support the hypothesis that an altered excitability status of cerebral cortex may be the link between migraine and epilepsy. As migraine is frequently underdiagnosed and undertreated in epileptic patients [19] and considering the risk of OLE mis-

diagnosis, the presence of each disorder should raise the suspicion of the possible presence of the other.

Pathophysiologic relations between migraine and epilepsy

Similar mechanisms in these disorders are kindling/central sensitisation and neuronal hyperexcitability.

Kindling *vs*. sensitisation

Kindling is the phenomenon by which repetitive induction of epileptic fits makes the cortex more excitable to the stimulus. The rat amygdala kindling is the best known experimental model of epilepsy [29]. This process can be involved in progressive worsening of epileptic syndromes and may account for refractoriness to treatments observable in up to 40% of patients [30].

On the other hand, painful sensitisation of trigeminal and thalamic sensitive neurons has been suggested as the mechanism of cutaneous allodynia [31]. This mechanism, documented after chronic exposure to opiates [32], may be involved in "medication overuse headache", a migraine-related condition associated with excessive use of acute treatment compounds, characterised by the progression of attack frequency up to a daily chronic headache and by a poor response to treatments [33].

Cortical hyperexcitability in migraine

If no doubt exists about the role of focal or generalised hyperexcitability in epileptogenesis, the concept of cortical hyperexcitability as a pivotal factor in migraine is more recent. Welch et al. [34] proposed that an altered excitability status of occipital cortex may be an important pathogenic factor for migraine, probably lowering the threshold for the development of cortical spreading depression (CSD), the neurophysiologic event underlying MWA. In recent years more lines of evidence supported the existence of such an altered excitability state, in both migraine with and without aura [35, 36]. Hypothesised mechanisms include impaired mitochondrial metabolism, derangement of ion channels and reduced magnesium levels [37].

Hyperexcitability: the pathogenetic link between migraine and epilepsy

If the bidirectional comorbidity between migraine and epilepsy were sustained by a shared neuronal hyperexcitability, thus a functional interference between CSD and epileptic discharges should be observed at experimental level. A study on human epileptic brain tissue found a higher network excitability induced by elevated K+ extracellular concentration, a condition knowing to occur as a result of CSD [38]. Moreover, experimentally induced CSD in human neocortical slices was able to induce sharp potentials [39]. These findings strongly suggest that a reciprocal facilitating interference represents the pathogenic link between migraine and epilepsy and may account for the epidemiological association of these diseases.

The rationale for antiepileptic drugs (AEDs) in migraine

Due to the above considerations, it is not surprising that certain AEDs acting by modulating neuronal function are effective in the prophylactic management of migraine, confirming the pathogenetic link also from a clinical point of view. At present the efficacy of topiramate and valproate in migraine prophylaxis is confirmed by a number of randomised controlled studies [40–43]; nonetheless emerging evidence indicates that lamotrigine [44], gabapentin [45], levetiracetam [46] and zonisamide [47] may be effective as well. AEDs are effective in migraine therapy probably because they act on brain excitability: topiramate reduces CSD in rat brain [48]; in a magneto-encephalographic study the neuronal excitability was reduced after a 30-day sodium valproate treatment [36].

Conclusions

Epilepsy and migraine remain two substantially different diseases, probably showing more differences than similarities. A shared neuronal hyperexcitability may be the pathophysiological link accounting for their bidirectional comorbidity and for the efficacy showed by AEDs in migraine. If the exposure to the side effects profile of AEDs appears to be always justified in epileptic patients, in migraine subjects the risk/benefit ratio of an AED prophylaxis should be individually assessed.

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