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Migralepsy

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Abbreviations: CSD: Cortical Spreading Depression; ILAE: International League Against Epilepsy

Introduction

Migralepsy is defined as a migraine triggered seizure [1], however the relationship between the two clinical entities is complicated. The term 'migralepsy' was introduced by Lennox and Lennox in 1960. It is a term used to describe a syndrome wherein ophthalmic migraine i.e. migraine with aura is followed by symptoms characteristic of epilepsy [2,3].

It is difficult to make a definite diagnosis of migraine (phenotypically heterogenous) as there are no objective tests and markers. This has resulted in a marked variability in prevalence studies. Migraines affect 15% of the population, with females having a greater prevalence than men [1], mostly aged 35-45. Epilepsy is estimated to occur in 1 in 26 people, with the incidence being highest in the first year of life and over the age of 75 [1].

Among epilepsy patients the prevalence of migraine is 7-26% and in migraine patients, epilepsy was prevalent in 1-17% [3]. With both conditions being common, there has been evidence to back up the assumption that migraines and epilepsy are co-morbid conditions. Ottman et al illustrated that the rate of migraines was significantly higher in patients with epilepsy (26%) and their relatives with epilepsy (24%) compared with the relatives without epilepsy (14%), with the relative risk being 2.4 [4]. Children with benign rolandic epilepsy have been shown to have increased risk of migraines as demonstrated by Giroud et al compared with children with absence epilepsy, partial epilepsy and head trauma [5]. However, Wirrell found there was no statistically significant difference between benign rolandic epilepsy compared with cryptogenic partial epilepsy [6]. Similarly, juvenile myoclonic epilepsy is also associated with increased incidence of migraine, a RR of 4.4 [7]. Ludvigsson found that a history of migraine with aura was a risk factor for developing epilepsy whilst migraines without aura did not have the same association [8]. Findings have not been consistent across all studies. Ottman, et al. [4] surveyed 2000 patients with epilepsy and their families and failed to show patterns of migraine and epilepsy. Another study in Norway did not demonstrate a significant correlation between epilepsy and migraine.

Possible Pathophysiology of Migralepsy

A common underlying mechanism has been suspected as many diseases are expressed as both seizures and headaches. Mitochondrial diseases in particular MELAS and POLG1 mutations can manifest with both epilepsy and migraines. In MELAS, the posterior cerebral region is preferentially affected [9] whilst POLG1 mutations result in epilepsy affecting the occipital lobe [10]. Damage in these regions may be related to the development of migraines. Familial hemiplegic migraine has been linked with mutations in the CACNA1AM, ATP1A2 and SCN1A channels; these are also closely linked to epilepsy [11].

Cortical spreading depression (CSD) was a concept initially proposed by Lashley in 1941. In the 1970s, glutamate released from glial cells was recognized as triggering CSD [12]. Although the mechanism and spread of CSD is not fully understood, the concept of hyper-excitability and synchronicity is basis for a common mechanism between epilepsy and migraines to exist. It has been hypothesized that seizure discharges in the occipital lobes trigger a genuine migraine headache through cortical spreading depression (CSD) leading to activation of the trigeminovascular system or brainstem mechanisms without any other associated cortical epileptic sign, as suggested previously [13]. The central autonomic systems; whether cortical or subcortical, have a lower threshold for epileptogenic

activation than those that produce a focal cortical sensory-motor semiology. This may explain why it is more likely to observe epileptic patients with post-ictal headache rather than migraine subjects with epileptic seizures [13] as the onset of seizures may lead to the onset of CSD to a greater degree as compared with the onset of CSD leading to seizures.

As AEDs can be used to prevent migraine, this further emphasizes a shared pathophysiology. Topiramate and Sodium Valproate are perfect examples of drugs that are also used for migraine prophylaxis as well as gabapentin and pregabalin. Zonisamide and levetiracetam have also been used in some case series reported. On the other hand, many AEDs are ineffective in preventing migraines suggesting alternative mechanisms to initial hyper-excitability may play a role.

Is Migralepsy a separate entity?

Occipital lobe epilepsy, primarily occurring in children, often presents as headaches as part of the ictal semiology. Visual auras and ictal headaches are not exclusive to occipital epilepsies. Panayiotopoulos hypothesized occipital lobe seizures triggered migraines by activating trigeminovascular or brainstem systems as discussed previously [14]. He describes visual symptoms which were distinct from migrainous auras, but postictal headaches consistent with migraine headaches. He also concluded that the quality of the visual aura could help distinguish between the two clinical entities. Elementary visual hallucinations were unique to epilepsy whilst wavy lines, zig zag patterns were well described migrainous auras not part of epilepsy aura. Epileptic visual auras were also noted to be shorter in duration.

Marks studied 79 patients with epilepsy and migraine; identifying [13] patients whose seizures and migraines were temporally related. In 5 of these patients, EEG showed periodic lateralized epileptiform discharges that resolved with the headache. Small case series and some case reports have demonstrated examples of patients with seizures triggered by migraine. Niedermeyer described 8 patients with generalized tonic clonic seizures occurring with migraines with preceding visual auras [15]. Interictally, imaging, examination and neurophysiology were all essentially normal. A positive family history of migraine was also associated and poor responses to migraine and epilepsy drugs were noted. Colombo et al reported a case of migralepsy meeting the ICHD-II definition; the patient suffered a GTCS following a typical migrainous aura [16]. An EEG obtained at the time showed right temporal epileptiform discharges, which normalized when the headache was not there. Topiramate was started to good effect.

Evidence against

Migralepsy has also been described without symptoms of aura. Freidenberg discusses a case where the patient suffered a GTCS during a typical migraine without aura [17]. The patient suffered a seizure arising from sleep after the 4th day of headache and left visual neglect. The MRI showed enhancement in the right parieto-occipital region, which resolved on repeat imaging. Verotti, et al. [18] summarized 16 potential cases in a multi centre review. Many of these cases did not meet the ICHD-II definition and did not have sufficient EEG data to rule out ictal headache. These cases demonstrated a female predominance but no consistent seizure localization or EEG pattern [18]. The author argued that these cases support a diagnosis of ictal headache, without any EEG representation, and the need for a greater understanding is needed before migralepsy can confidently be its own entity [18].

Migraine is listed in 'the Borderland of epilepsy'. Gowers recognizes that migraine 'hemicrania' is difficult to differentiate from epilepsy. He also stresses two symptoms that are particularly discriminative; migraine headache is much more severe than postictal headache and visual symptoms are short in epilepsy and long in migraine. Panayitopolus concluded that the duration of visual symptoms is key in recognizing whether the symptoms are related to migraine or occipital lobe epilepsy even if these are not followed by headache or an epileptic seizure [14,19].

More commonly epilepsy rather than headache specialists show interest in migralepsy. Despite this, migralepsy as such appears in the headache classifications and not in epilepsy classificiations [3,20]. Migraine triggered seizures have been included in the ICHD-II as a complication of migraine, whilst international league against epilepsy (ILAE) seizure classification does not mention migralepsy at all. The 2013 international classification of headache disorders included migraine aura triggered seizures; which required 'migraine fulfilling criteria for migraine with aura' and 'a seizure fulfilling diagnostic criteria for one type of epileptic attack and occurring in a patient with migraine with aura, and during, or within 1 hour after, an attack of migraine with aura' [21]. However, the international league against epilepsy proposed terminology for seizures did not specifically include migralepsy as a seizure type [22].

The concept of migralepsy as a migraine-epilepsy sequence has been criticized by many authors as they felt most of the cases reported did not follow an unequivocal migraine-epilepsy sequence [2]. They felt these were occipital seizures imitating migraine with aura. Thus 2 out of 3 cases described by Lennox seemed to have occipital epilepsy with visual hallucinations23. Sances et al. [23] reviewed 50 potential migralepsy cases and found only two cases met the criteria outlined by ICHD-II23. They described a patient complaining of visual symptoms associated with déjà vu sensation, olfactory hallucination lasting about ten minutes, which developed into a GTCS. Although the symptoms described are migrainous in origin, as confirmed by a visual aura rating scale of 6, all of his symptoms as well as those typical of visual aura, could have represented an epileptic aura that may develop into a seizure.

Migraine and epilepsy have common pathophysiologic mechanisms and share some defining characteristics;

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distinguishing them from other neurological disorders i.e. they are both episodic2. However, on clinical grounds alone it can be hard to differentiate between the two. Epileptic seizures and migraine attacks may easily be mistaken for each other and can overlap. There are marked difficulties in distinguishing epileptic occipital aura from migraine aura especially if there is limited history regarding the visual disturbance [24].

Definitions include

a. "Migraine visual aura starts as a flickering, uncoloured, zig zag line in the centre of the visual field, progressing over 4-30 min towards the periphery of one hemifeild, and a scotoma often follows. The total duration is about 60 minutes"

b. "Ictal elementary visual hallucinations of occipital lobe epilepsies are mainly coloured and circular, develop rapidly (within seconds), and are relatively brief (2-3 min). They often appear in the periphery of a temporal hemifield, widen and multiply during the seizure, and frequently move horizontally towards the contralateral side".

However, this is rarely clear in clinical practice. Visual symptoms may be mixed, and brief visual seizures may be followed by headache and vomiting, thus making them indistinguishable from migraines. Alternatively, headaches could be an ictal phenomenon [3,20].

The international classification of headache disorders included the term hemicrania epileptica [21]. Hemicrania epileptica is recognized as an ipsilateral headache with migraine features occurring as an ictal manifestation of seizures. Isler et al. [25] found that hemicranial attacks of pain coincided with seizures activity and lasted for seconds to minutes. Although this condition is rare, it has been included in the ICHD-II =:The diagnostic criteria included: "

1) headache lasting seconds to minutes with features of migraine;

2) the patient is having a partial epileptic seizure, and either

a) headache has significantly improved immediately after the partial seizure has terminated, or

b) headache is ipsilateral to the seizure discharge [21].

Diagnosis requires the simultaneous onset of headache with EEG-demonstrated discharge [25]. On the other hand, the 2001 international league against epilepsy glossary included 'cephalic' as a non-motor, sensory manifestation e.g. light-headedness, tingling or headache [26].

A case series of 5 patients demonstrated migraine/headache that lasted longer than 'seconds to minutes' and was the only clinical manifestation of a non-convulsive status epilepticus [24,27,28]. Of note, these patients did not meet the above mentioned criteria for HE. Headache with migraine features is a common post-ictal phenomenon occurring in 50% of patients with epilepsy. This has also been included in the ICHD-II. Schon and Blau reported 51% of epileptic patients having post-ictal headache. PIH was linked more with GTCS than with focal seziures. PIH has been reported more often in symptomatic epilepsy but it is mainly observed in idiopathic occipital seizures [18].

Both interictal and ictal EEG abnormalities in patients with migraine consist mainly of asymmetrical theta bursts, located over the temporo-occipital area. Patients with epileptic visual symptoms may also show similar EEG abnormalities. EEG recordings may thus only record theta or delta waves, reflecting the subcortical abnormalities. Photophobia is mentioned only sporadically in epilepsy; only about 5% have seizures triggered by visual stimuli13. Occipital seizures can rapidly propagate to the temporal lobes, explaining why parieto-occipital seizures have predominant autonomic symptoms and can be mistakenly diagnosed as migraine. A recent study by Toldo et al. showed that 56 of 1795 children had both headache and epilepsy, commonly migraine. In 44%, the onset of epilepsy preceded headache, in 27% headache started first whilst in 29% both started in the same year [18].

Future research aims

Chromosome 9q, 14q and 12q have been deliberated by deprez and polvi [29,30]; the loci being linked to both epilepsy and migraine, however to the present date no causative genes or probability loci in 'migralepsy' have been identified.

Migraine as a sole manifestation of a seizure might be the expression of a non-convulsive SE, which may only be diagnosed by EEG recordings. High-voltage, rhythmic, 11-12 Hz activity with intermingled spikes over right temporo-occipital regions, high voltage theta activity, intermingled with sharp waves over occipital region and bilateral continuous spike and slow-wave discharges have been associated with IEH. In patients with IEH it was noted a complete remission of the headache was obtained with IV diazepam and not with antimigraine drugs. MRI brain in these patients showed secondary brain lesions in the right temporo-parieto-occipital region [2,28] with a restricted diffusion in the right occipital region or enlarged sulci in the right parietal region. Therefore, further research should be done with MRI imaging in patients presenting with symptoms suggestive of migralepsy; to be able to identify any characteristic MRI findings.

There is a role for 24-h video EEG telemetry recordings as demonstrated by Mark and Ehrenberg. They looked at two patients in which the entire migraine-epilepsy sequence was captured, showing changes during the migraine that were atypical for electrographic epilepsy. During migraine aura, bursts of spike activity may appear similar to ictal EEG. However, in most reported cases the EEG does not show the usual evolution temporally with progressive increase and declines in the frequency and amplitude of rhythmic, repetitive epiliptiform

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activity typical of ictal EEGs in epilepsy. A migraine attack can originate at either a cortical or subcortical level, whilst epilepsy generally arises cortically and can only be sub modulated at the subcortical level.

IEH is associated with other epileptic manifestations such as ictal-sensory and motor features more frequently than literature suggest. Therefore, an ictal EEG is recommended during a migraine attack even in patients not known to suffer from epilepsy, despite the fact that it is not always possible to detect an ictal epileptic manifestation only by scalp EEG recording. More research is required in this area and ictal EEG to become more readily available.

Conclusion

Due to diagnostic uncertainty the existence of migralepsy has been questioned often. The lack of published data highlights the inadequacy of the current definitions of ICHD-II about temporal and/or clinical link and overlap between migraine and epilepsy [2]. The concept of migralepsy in accordance to current definitions is too narrow and inadequate and needs revision. It has been suggested migralepsy could often be a simple seizure starting with an ictal epileptic headache followed by a sensory-motor partial or generalized seizure [3,20]. On the contrary there is suggestion that headaches may be the sole representation of an epileptic seizure [2,25,27,28].

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