Postictal headache in epileptic patients

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Received: June 02, 2014
Published online: September 10, 2014

The International Classification of Headache Disorders-third edition beta (ICHD-3 beta), defines the postictal headache as “headache caused by and occurring within 3 hours after an epileptic seizure, and remitting spontaneously within 72 hours after seizure termination”. People at highest risk of suffering PIH are who have generalized tonic-clonic seizures (GTCSs) and a history of interictal headaches. An occipital epileptogenic focus may be an additional risk factor. Also PIH frequently have characteristics of migraine, the diagnostic criteria of “headache with features of tension-type headache or, in a patient with migraine, of migraine headache” in ICHD-2 has been ruled out from the ICDH-3. The high percentage of PIH in patients with epilepsy which really burden patient's daily life. For purposes of comparison, trials should adhere to a unified definition of PIH, and ICHD-3 beta revised the ICHD-2 definition which widens the inclusion criteria to any headache attributed to a seizure and following it. In order to improve the diagnosis and management of this symptom, clinicians should pay more attention to epileptic patients with PIH.

Keywords: epilepsy; postictal headache; migraine

Introduction

Co-morbidity of headache and epilepsy, although still under debate, is well known for more than a century. In the International Classification of Headache Disorders, third edition beta (ICHD-3 beta) [1], postictal headache (PIH) is defined as “headache caused by and occurring within 3 hours after an epileptic seizure, and remitting spontaneously within 72 hours after seizure termination”, as a type of headache attributed to epileptic seizure. The diagnostic criteria has some different from ICHD-2 [2], which ruled out the characteristics of headache—“headache with features of tension-type headache or, in a patient with migraine, of migraine headache”. Table 1 showed the detail of diagnostic criteria.

The percentage of those with PIH ranges between 12% and 52% [3-5], implying that PIH adds an additional significant burden to persons with epilepsy in addition to actual seizures. We have investigate the incidence of PIH and the factors potentially related to the occurrence of PIH in a Chinese epileptic center, from Feb. 01, 2012 to May 10, 2013, which based on the guideline of ICHD-II. PIH occurred in 328 (38%) of the subjects, and the incidence of PIH in occipital lobe epilepsy (OLE, 56%) was significantly higher than in temporal lobe epilepsy (TLE, 35%) and frontal lobe epilepsy (FLE, 39%). After generalized tonic-clonic seizures, PIH appears more frequently than other types. Age at onset, seizure types and epileptic classification were each significantly related to the PIH incidence, by the Logistic regression analysis [6]. The results of our study revealed possible relationships between PIH and epileptic focus region and epileptic discharges spreading area.

Why ICHD-3 beta changed the diagnostic criteria for 7.6.2 PIH? What advanced results from recent studies? The available clinical reports have focused on various characteristics of the headaches and their treatment, on
associations with demographic and epilepsy-specific factors, and on their correlation with interictal headache. No study has specifically addressed the pathophysiological mechanisms leading to PIH. However, much progress has been made over the last decade in understanding the processes occurring in the postictal state [7] and those underlying the occurrence of headache, especially migraine [8]. Here, we review recent advances in PIH in epileptic patients, which focus on the risk and the possible mechanisms of PIH, and make sure and understand deeply the reason for the change of diagnostic criteria.

1 Risk factor for PIH

Postictal headaches occur after most seizures, suggesting that specific seizure-related and/or patient-related factors may interact and lead to their occurrence.

1.1 Age

Our study showed that patients with PIH were significantly younger than patients without PIH, and logistic regression analysis revealed that age at onset was significantly related to the occurrence of PIH, which was similar with some other studies [3]. But Forderreuther et al [4] and Cai et al [9] did not find a significant association between age and risk of PIH. HELP Study Group studies [5] have reported the association between younger age and seizure-related headaches (86% of them had PIH). Syvertsen et al reported the association between younger age and headaches (68% had PIH) [10].

However, some studies that addressed pediatric population found a lower prevalence of PIH (12-36%) [9, 11, 12] than in most adult studies (30-52%) [13, 14]. In 2011, Verrottiet al conformedi [13] a cross-sectional multi-center study, which includes 1,264 epileptic children. They selected 142 children who had periictal and/or interictal headache, which showed that postictal headaches were most frequent (62%), 93% of preictal and 81% of postictal headaches presented as migrainous features.

The relatively low prevalence of PIH in the pediatric population may be explained by their shorter history of epilepsy and lower treatment resistance compared with adults. Many studies of adult patients included patients with histories of epilepsy exceeding 15 years [8,13,14,16,17] and patients with drug-resistant seizures, suggesting that certain characteristics of epilepsy and its treatment may have a greater influence on the occurrence of PIH than age.

Moreover, the proportion of patients with PIH who also have interictal headache (IIH) has been reported to range widely from 27% to 71%. These associations also may be age specific. In a pediatric population, there was no correlation between IIH and PIH and no tendency for children with IIH migraine to have migrainous PIH [9].

Similarly, another study reported that children with migraine did not increase the risk of PIH than the children with tension-type headache [11]. Interestingly, no association has been found between family history of headaches or migraine and PIH.

From the present studies, it would be hard to determine the definite relationship between postictal headache and age.

1.2 Interictal headache

The occurrence of interictal headache (IIH) appears to increase the risk for PIH [3], and pain characteristics are reported to be similar in a given individual [16, 18]. However, our logistic regression analysis did not find that a history of interictal headaches was significantly related to the occurrence of PIH [6].

Velioglu and colleagues [19] observed that patients with migraine were significantly more likely to have intractable seizures and to require antiepileptic drug polytherapy for seizure control than patients with epilepsy without migraine. However, Toldo [11] and Yamane [20] reported that headaches began predominantly either in the same year of the epilepsy onset or after the epilepsy, which indicated the inverse causal relationships between IIH or migraine and epilepsy or shared neuropathological

Table 1. Diagnostic criteria for 7.6.2 PIH in ICHD-3 beta and ICHD-2

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<thead>
<tr>
<th>ICHD-3 beta diagnostic criteria</th>
<th>ICHD-2 diagnostic criteria</th>
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<tr>
<td>A. Any headache fulfilling criterion C</td>
<td>A. Headache with features of tension-type headache or, in a patient with migraine, of migraine headache and fulfilling criteria C and D</td>
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<tr>
<td>B. The patient has recently had a partial or generalized epileptic seizure</td>
<td>B. The patient has had a partial or generalized epileptic seizure</td>
</tr>
<tr>
<td>C. Evidence of causation demonstrated by both of the following 1. headache has developed within 3 hours after the epileptic seizure has terminated 2. headache has resolved within 72 hours after the epileptic seizure has terminated</td>
<td>C. Headache develops within 3 hours following the seizure</td>
</tr>
<tr>
<td>D. Not better accounted for by another ICHD diagnostic criteria</td>
<td>D. Headache resolves within 72 hours after the seizure</td>
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mechanisms. Indeed, the bidirectional influences between IIH and epilepsy in general and PIH in particular are complex. Epidemiological studies are further complicated by the relatively high prevalence of both headaches and epilepsy in the general population. Additionally, in light of the above-mentioned available data, the ICHD-2 definition strongly linking the type of PIH to the type of IIH has been revisited by ICHD-3 beta [1].

1.3 Characteristics of seizures: GTCSs

In our group, PIH appears more frequently after GTCSs, which was similar with many other studies [13, 16, 17, 21], which reported the PIH in 28%-96% of patients with primary GTCSs and in 42%-88% of patients with secondary GTCSs. For example, Schachter et al. reported that PIH occurred in 96% of their 44 patients with GTCSs, 36% of 238 patients with complex partial seizures (CPs), and 55% of 71 patients with both GTCSs and CPs [17].

However, Yamane [12] reported no correlation between PIH and seizure type, which come from a children study. Fordehreuther [4] also showed that 43% of 53 patients after partial seizures without generalization reported PIH. More specifically, some patients with CPs without secondary generalization also had PIH. Simple partial seizures were usually either not associated with PIH or had a relatively low association (13%) with seizure-related headache (86% had PIH).

Interestingly, Ito [3] found that secondary GTCSs were significantly associated with nonmigrainous PIH. The reason is still not clear, one explanation is that generalization of GTCSs may trigger some other pathophysiological changes.

1.4 Localization of epileptic focus

Our result suggested that the incidence of PIH in OLE was significantly higher than in FLE and TLE. More extensive efforts have been made to study the correlation between PIH and lobar localization of focal epilepsy, particularly in children, between occipital lobe seizures and headaches [22-24], which observed a relatively high occurrence of PIH in patients with presumed OLE. Ito et al., in a series of surveys, found PIH to be significantly more frequently in patients with clinical OLE (59-62%) than in their counterparts with either TLE (23-41%) or FLE (40-42%) [3,13,14]. One possible explanation in patients with partial epilepsy, that the occipital lobe may play a key role in the PIH’s pathophysiology. However, no association could be found between PIH and either lobar localization based on clinical, EEG, and imaging data in a cohort of 597 patients with epilepsy [5].

The brain structure most responsible for the migraine is the occipital lobe [25, 26]. The posterior temporal locate very close to the occipital lobe, and there are abundant anatomic connections between the temporal structures and occipital cortices. When both the occipital cortices and temporal cortices are firing, patients could present the migraine symptoms.

2. Characteristics and Pathophysiology of PIH

PIH can present as migraine, TTH or other unclassified type of headache. Previous reports have pointed out that about 41-56% PIH has similar symptoms to migraine such as accompanying photophobia, nausea and phonophobia [27,28]. These studies indicate that migraine and migraine-like PIH may have some common underlying mechanism, which have not been clarified.

Several studies had suggested that cortical spreading depression (CSD) and epileptic focus might facilitate each other. Occipital neural activity can spreads forward across the cortical surface, and subsequent cortical blood flow reduction is likely related with migraine [29,30]. Some studies from fMRI and positron-emission tomography (PET) had shown the blood flow changes during migraine attack [31, 32]. Bowyer [33] performed magnetoencephalographical(MEG) study and found that neuroelectrical activity in not only the occipital lobe but also in the temporal structure, during migraine aura. Changes in blood flow and regional cerebral diffusion [34], suggestive of the trigeminovascular processes described in patients with migraine, have been reported following epileptic seizures.

Finally, the discovery of mutations (usually affecting the Na/K-ATPase or sodium channels but also, less frequently, calcium channels) causing hemiplegic migraine and epilepsy in affected individuals provides a common biological link between these two conditions [35,36].

3. Treatment of PIH

In our group, no patient treated headache according to a medical prescription or used over-the-counter analgesics. Several other studies have reported the use of analgesics by patients with PIH. Most patients used over-the-counter analgesics, such as aspirin, and acetaminophen, and only 4% and 11% in another were prescribed anti-headache medications by their physicians [10, 37]. However, a relatively small percentage of people with PIH are taking analgesics or being prescribed medications by their physicians, which probably reflects the neglected status of the PIH entity within the medical community. In addition, two case reports showed that
sumatriptan was able to terminate acute migraine-like postictal headaches [24, 38]. There are well known that some AEDs (valproate and topiramate) can be used for migraine prophylaxis [39]. However, the extent to which particular AEDs affect PIH has not been specifically studied, which need the further prospective studies to test these drugs efficacy.

As the above information, with the high percentage of PIH in patients with epilepsy, PIH really burden patient’s daily life. For purposes of comparison, trials should adhere to a unified definition of PIH, and ICHD-3 beta revised the ICHD-2 definition which widens the inclusion criteria to any headache attributed to a seizure and following it.

Conclusions

According to the available data presented in this review, people at highest risk of having PIH are who have GTCSs and a personal history of interictal headaches. An occipital epileptogenic focus may be an additional risk factor. The high risk of having PIH, especially after GTCSs, may help differentiate epileptic from clinically similar nonepileptic psychogenic.

As the high percentage of PIH in patients with epilepsy, PIH really burden patient’s daily life. For purposes of comparison, trials should adhere to a unified definition of PIH, and ICHD-3 beta revised the ICHD-2 definition which widens the inclusion criteria to any headache attributed to a seizure and following it. Our hope is that this article will direct clinicians to pay more attention to epileptic patients with PIH and will therefore improve the management of this symptom. Although it is difficult to study headache in animal models, the development of modern noninvasive investigational tools in humans, such as functional imaging and diffusion-weighted MRI, may facilitate future research aimed at uncovering brain mechanisms underlying PIH, as well as other postictal symptoms.

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