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HOT TOPICS IN PAIN AND HEADACHE (N ROSEN, SECTION EDITOR)

Painful Seizures: a Review of Epileptic Ictal Pain

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Abstract

Purpose of Review To summarize the literature regarding the prevalence, pathophysiology, and anatomic networks involved with painful seizures, which are a rare but striking clinical presentation of epilepsy.

Recent Findings Several recent large case series have explored the prevalence of the main cephalgic, somatosensory, and abdominal variants of this rare disorder. Research studies including the use of electrical stimulation and functional neuroimaging have demonstrated the networks underlying painful somatosensory or visceral seizures. Improved understanding of some of the overlapping mechanisms between migraines and seizures has elucidated their common pathophysiology.

Summary The current literature reflects a widening range of awareness and understanding of painful seizures, despite their rarity.

Keywords Ictal · Pain · Somatosensory · Abdominal · Headache · Seizure

Introduction

Epileptic ictal pain is a rare phenomenon which is classically categorized as mainly cephalic, abdominal, or unilateral (truncal or peripheral) in location and is mostly seen in the setting of focal onset seizures [1, 2]. While post-ictal headaches are common in patients with epilepsy (PWE), true ictal epileptic headaches (IEH) which are brief, paroxysmal, and cease upon termination of seizure, particularly in isolation of other neurological symptoms appear to be infrequently encountered. It has been reported that the frequency of ictal pain of any type ranges from 0.2 to 2.8% of PWE overall, with rates as approaching 4.1% in patients specifically with focal epilepsy syndromes [1, 2•, 3•, 4, 5].

Clues to pain being of an ictal nature may include their relatively brief and abrupt stereotypical paroxysmal occurrence. Other indicators may include associated phenomena such as confusion or loss of awareness, clonic activity, and abnormalities on electroencephalogram (EEG). Response to empiric anti-epileptic drug (AED) therapy might be a helpful feature, though not specific. Ictal pain may be a diagnostic challenge as it may occur in isolation, unaccompanied by other clinical findings. In addition, there may be an emotional reaction to the pain leading to vocalization or crying out which may appear somewhat bizarre. To complicate matters, focal sensory seizures with preserved awareness may transpire with little or no electrographic correlate. These features may potentially result in erroneous or delayed diagnosis. Therefore, familiarity with this clinical entity is important to enable rendering appropriate care to this patient population. The key features of the three subtypes of ictal epileptic pain are summarized in Table 1.

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Headache as a Symptom of Seizures

Description

Cephalgia is commonly seen as a symptom in association with epilepsy and is logically categorized as pre-ictal, ictal, post-ictal, or interictal. However, the relative prevalence of each these types of seizure associated headaches is somewhat difficult to ascertain in the literature, likely due to variations in definitions, clinical features, performance of EEG, and antiquated nomenclature. Efforts continue to standardize terminology and classification. The 2018 edition of the *International Classification of Headache Disorders* (ICDH-3) recognizes headaches associated with epilepsy as migraine

Table 1 Ictal epileptic pain subtypes

Description	Characterization	Localization
Ictal epileptic headache	May be migrainous, tension type, or neuralgiform	More frequently described with posterior epileptic foci, but also in cases with generalized discharges. Seizures may occur in association with cortical spreading depression
Somatosensory pain	May be burning, stabbing, prickling, throbbing, or tearing sensations	Seizure discharges most likely involving the parietal operculum or insula, though cases of epilepsy with foci originating in the parietal and temporal regions have been described
Abdominal pain	Sharp sensations or visceral colic	Temporal and parietal foci described most commonly. Amygdala or insula are plausible

aura-triggered seizure, IEH occurring during a focal seizure and remitting soon after, and post-ictal headache [6••]. Migraine aura-triggered seizure, also known as migralepsy, which is a focal seizure preceded within an hour by an attack of migraine with aura, is seen rarely, as only a few cases have been reported in the literature [7, 8]. A multicenter retrospective study of 4600 children with epilepsy found only 16 cases [9]. In the absence of concurrent EEG, it may be difficult to determine if migraine aura symptoms are potentially the early manifestation of seizure or if migraine is in fact the inciting event. In regard to IEH, the ICHD-3 proposes that a headache should be ipsilateral to the concurrent seizure discharge and/or terminate with seizure cessation. IEH, which also encompass the variant described as hemicrania epileptica, are typically short in duration, as most seizures tend to be brief. However, epileptic status migrainosus due to prolonged electrographic seizures have been described in rare case reports [8, 10]. A history of seizures or focal lesions on neuroimaging appeared to have prompted the request for diagnostic EEG in these unique cases. Lastly, the ICDH-3 defines post-ictal headache as occurring within 3 h of a seizure and lasting up to 3 days duration. The ICDH-3 classification of seizure-related headaches is summarized in Table 2.

The most common type of epilepsy-related headache is post-ictal. The reported prevalence is between 10 and 50% in PWE depending on the ascertainment method and diagnostic criteria [11, 12]. In standardized interviews of 100 medically refractory PWE, peri-ictal headache was self-reported in 47%, mostly post-ictal headache. Eleven percent of patients reported pre-ictal headaches, defined in this study as occurring up to a day prior [13]. Peri- or post-ictal headache in this series were felt to have some lateralizing value for the seizure focus in temporal lobar epilepsy but not in other seizure types. Another study of 110 PWE showed that 43% reported headaches which were associated with epileptic seizures, of which the majority had exclusively post-ictal headaches. Only 3 patients had both pre- and post-ictal headaches together, and just a single patient reported pre-ictal headaches alone. The most commonly reported headache types overall were post-ictal migraine and tension-like headaches, each accounting for about a third of classifiable types [5]. Recent studies of similar design utilizing structured interviews reveal similar data. In a retrospective cohort of 388 PWE, pre-ictal headache up to 24 h prior to a seizure was reported in 6.7% of PWE, ictal headache in only 0.8%, and post-ictal headache was observed in 19.1% [12].

IEH as the main feature or sole manifestation during an active seizure appears to be a rare phenomenon occurring in 3–5% of PWE or fewer [11]. One retrospective analysis of the EEG recordings of nearly 4800 patients admitted to the epilepsy monitoring unit (EMU) revealed headache during the active seizure in only 5 patients [11]. These were described as either tension type or migrainous in character and terminated immediately with seizure cessation. IEH may be neuralgiform in character and mimic other headache types [14]. Similarly, a retrospective review of 831 consecutive PWE admitted to the EMU, revealed headache as an aura of seizure in only 6 patients, or 0.7% [15]. A 2017 review by Cianchetti et al. identified only 32 cases in the literature since 1971 of IEH as defined as head pain caused by a simultaneous epileptic discharge, occurring in isolation or preceding other epileptic symptoms [7]. Accompanying symptoms were described in half of the patients including photo- or phonophobia, nausea, pallor, difficulty talking, agitation, and irritability. Visual symptoms were also reported. The location of pain did not appear to have good localizing value in terms of focus of lesion or seizure in this review, though the committee on the ICHD-3 has judged this to be a useful diagnostic feature.

Table 2 Headaches associated with seizures. Adapted from the International Classification of Headache Disorders, 3rd edition

ICHD-3 code	Description	Criteria
1.4.4	Migraine aura-triggered seizure	Focal seizure within ≤ 1 h of a migraine with aura
7.6.1	Ictal epileptic headache	Occurs concurrently with a focal seizure discharge and is ipsilateral to the ictal discharge or terminates with seizure cessation
7.6.2	Post-ictal headache	Occurs ≤ 3 h of a seizure and lasts ≤ 3 days

Pathophysiology

There appears to be a bidirectional relationship between migraine and epilepsy. While PWE frequently experience headaches, epilepsy is also observed to occur at least 2.4 times more commonly in migraineurs than in the general population [16]. It has been inferred that the pathophysiology of post-ictal headaches is associated with migraine, as patients often have clinical characteristics such as photophobia, phonophobia, or vomiting [13]. Migraines and seizures are known to exhibit similar overlapping pathophysiological phenomena [17]. Studies have shown there to be an increase in cerebral blood flow in pain-sensitive pial arteries in both conditions, which has been attributed to broken autoregulation in decreased peripheral vascular resistance [13, 18]. Bearing witness to exposed cerebral cortex peri-operatively during seizures, early investigators noted ictal vasodilation in large pial veins over areas involving epileptic foci, concluding that the main mechanism of epileptic headaches was local vasodilation of large vessels and dura mater which then stimulate the trigeminovascular system (TVS) and sensory pain pathways [19]. Indeed, when EEG and fMRI are recorded simultaneously, there is an observable pattern of changes in regional blood flow which correlates to interictal epileptic spikes. Momentary increases in blood flow and metabolism at the site of a seizure focus are also seen on ictal single-photon emission computerized tomography or positron emission tomography. However, when observed more chronically, the location of spikes tends to correlate with decreased metabolism [20].

The leading hypothesis on the shared pathophysiology underlying both migraine and seizures is paroxysmal fluctuation in cortical neuronal excitability. In epilepsy, chronic hyperexcitability in a group of neurons intermittently transitions to hypersynchronous discharges in a greater population of cells, affecting ion membrane permeability and leading to seizure occurrence. Migraine is associated with cortical spreading depression (CSD), which is a slowly propagating wave of neuronal depolarization and transient hyperexcitability, during which auras are frequently observed, followed by neuronal suppression typically lasting minutes in duration. There is a brief increase in cerebral blood flow, followed by a more sustained reduction in perfusion. CSD activates the TVS and a subsequent cascade of inflammatory molecules, resulting in pain [21]. If the two processes overlap, then both seizure and migraine can occur at the same time together, or following one another within a short interval [20].

CSD may be initiated through the activation of presynaptic voltage-gated calcium channels, associated with increased intracellular calcium and extracellular potassium, which in turn release glutamate from cortical pyramidal cell synapses. NMDA-type glutamate receptors on pyramidal neurons are in turn activated, with transient hyperexcitability followed then by a more prolonged period of neuronal suppression [21, 22]. There may be a lower threshold to trigger the process of depolarization associated with CSD than for epileptic seizures. Thus, it is more probable for an epileptic activity to bring about peri-ictal migraine, than for the threshold to reach a sufficient level for initiation of seizure activity in conjunction with CSD, though it may conceivably occur as described in migraine aura-triggered seizures [22].

It is known that both epilepsy and migraine have a genetic predisposition. For example, familial hemiplegic migraine (FHM) is inherited in an autosomal dominant fashion. Mutations in any of the three FHM genes, CACNA1, ATP1A2, or SCN1A, can lead to seizures by alterations of ion channel function and neuronal membrane excitability [17, 21]. The mutations in the SCN1A gene are associated with infantile and adult forms of epilepsy, and illustrate one genetic link between migraine and epilepsy. PWE in the Epilepsy Phenome/Genome Project cohort with 2 or more first-degree relatives with epilepsy had a two-fold increase of risk in having comorbid migraine with aura [23].

Localization

EEG may be considered for patients with otherwise unexplained prolonged medically intractable headache, particularly if occurring in PWE or those suspected of having epilepsy. Video EEG may be critical for diagnosis, but aside from the actual recording of an IEH occurring concomitantly with a seizure on monitoring, the associated patterns may be relatively non-specific. IEH in isolation may also occur in the absence of overt EEG findings, as is the case for other types of focal aware seizures [7, 9]. Descriptions of EEG findings include 11–12-Hz activity and spikes over the right temporo-occipital, theta activity mixed in with sharp waves over the occipital regions, continuous spike and slow wave discharges bilaterally, and generalized discharges [24].

Several authors have proposed that seizures involving the occipital head regions may be more likely to activate headache, although they have also been observed with seizures localized to the temporal, frontal, and parietal lobes [5, 7]. A study based on clinical symptoms, EEG, and neuroimaging compared post-ictal headaches 109 patients with either occipital or temporal lobe epilepsy and found that a post-ictal headache occurred in 62% of the patients with occipital lobe epilepsy and 23% of those with temporal lobe epilepsy [25]. Generalized convulsions seem to be more often associated with post-ictal headaches than other seizure types. Children may experience seizure-associated headaches more often, perhaps reflective of more autonomic symptoms or susceptibility to headache in comparison with adults [11].

There is an observed association between childhood epilepsy with occipital paroxysms and migraine. Gastaut syndrome is rare and usually occurs in the first decade of life. Seizures start with visual symptoms such as scintillating

scotomas or other hallucinations, and eye deviation, then evolve into impaired awareness and focal motor activity. Notably, following a seizure, migraine headaches are very common. Panayiotopoulos syndrome also has predominantly occipital spikes on EEG. However, clinically, the patients are more often observed to have autonomic symptoms such as nausea, vomiting, lethargy, and syncope. Seizures are infrequent, but changes in consciousness and post-ictal migraine headaches do occur [20].

IEH in particular has been described with both focal and generalized epilepsy syndromes, though most cases are due to focal brain pathology and should be investigated accordingly [7, 11, 24]. They appear to affect any age group and either sex equally.

Treatment

The therapeutic plan for PWE should take into consideration the comorbidity of headaches. Since both migraines and seizures have a similar pathophysiology of CSD, the use of AEDs can be beneficial for headaches since many work mechanistically via ionic gradients or modulating gamma-aminobutyric acid activity [17]. Topiramate and valproic acid have been approved by the American Academy of Neurology and the American Society of Headache as AEDs for migraine prophylaxis. Accordingly, these are the preferred AEDs for patients suffering from both epilepsy and migraines, though there is little published data specifically addressing this topic. Other AEDs such as zonisamide, carbamazepine, oxcarbazepine, and gabapentin can also be considered as they have been suggested to have a role in the prevention of various headache types as well [16, 26]. Triptans and ergots have shown some effectiveness in treating patients with post-ictal migraines [5]. The effect of successful epilepsy surgery or implantable devices on peri-ictal headaches has not been clearly elucidated at this time, though presumably the reduction of seizure occurrence would likely be beneficial.

Somatosensory Pain as a Symptom of Seizures

Description

Painful somatosensory seizures (PSS) are rare, with their occurrence in intractable focal epilepsy estimated to be around 0.2 to 0.6% of patients evaluated in the EMU, and 1.5% of epilepsy cases specifically involving somatosensory seizures [2•, 3•, 27••]. One large retrospective review of 5133 patients investigated in the EMU found only 10 patients had documentation of epileptic ictal somatosensory pain [3•]. A similar retrospective review of 4736 PWE, identified merely 4 patients with primarily peripherally localized ictal pain [2•]. Onset may be at any age.

The specific sensations associated with PSS have been described as burning, stabbing, knife-like, prickling, throbbing, or muscle tearing in character [2•, 27••]. The pain may be so intense as to be associated with grimacing, screaming, or crying out. The sensations most often involve specific body parts, such as the limbs, but may be perceived as segmental. They typically occur contralaterally to the location of the cortical seizure focus but less commonly manifest ipsilaterally or bilaterally [3•, 27••]. Sporadic reports exist describing EEG-validated cases with unusual PSS presentations such as ictal chest, genital, facial, pharyngeal, and lingual pain [2•, 28–31]. Accompanying symptoms may include paraesthesias, thermal sensations, perceptual body distortion, and motor manifestations [18]. Of note, pain may also occur in reaction to focal tonic muscle contraction, which may be related to severe muscle spasm and should be distinguished from that of somatosensory origin [3•].

Localization

The network or "matrix" involved in PSS likely involves the primary sensory cortex (SI), the parieto-opercular secondary somatosensory region (SII), the insula, cingulate gyrus (CG), and lateral thalamus [32, 33]. Other areas may be associated including the amygdala, mesial fronto-parietal secondary somatosensory area (SSMA), motor cortex, and posterior parietal cortex. The widespread nature of the network may reflect the various neurologic functions involved with pain perception including sensation, attention, emotion, memory, motor, and autonomic components.

Most reports of PSS are based on individual cases, often with evidence for localization of seizures based on non-invasive imaging such as PET, SPECT, or MRI and scalp EEG data. A few cases of PSS have been described with intracranially verified electrographic recordings using various techniques used for surgical resection planning, including subdural grid or strip electrodes over the cortical surface or intracranial depth electrode implantation, known as stereoencephalography (SEEG). While recording from as close to cortical regions of interest as feasible, these methods may still be limited by the selective areas anatomically investigated. Resection of the epileptogenic zone with resolution of symptoms is considered a gold standard.

Some cases of PSS have been described in the setting of presumed parietal epilepsy. A case review of 604 consecutive cases of focal epilepsy found 6 patients with painful somatosensory auras, felt to be from either the parietal or temporal regions by scalp EEG and neuroimaging. It is possible that at least some of these cases may have included operculo-insular seizure onset or spread, which is difficult to discriminate by conventional surface EEG. The authors postulated spread to

the SII area as the reason for perceptions of pain in the temporal onset cases [4]. Another series found 3 out of 573 PWE evaluated in the EMU with PSS, in these cases felt to be localized to the parietal SI region based on more specific investigations including use of subdural grids and strips [18]. The SSMA was investigated in some patients, though SII would have been mostly inaccessible without depth electrodes or opening of the Sylvian fissure and may not have been sampled adequately.

Montavont and colleagues presented a case series of 5 patients with intractable PSS, analyzing their ictal recordings and electrical stimulation mapping (ESM) results during SEEG implantation [27••]. By correlating the clinical symptoms at the times where anatomically an ictal discharge was seen to manifest or propagate, thus they made a compelling argument for PSS to be more likely to be arising from the involvement of the operculo-insular cortex, including SII, as opposed to SI. Electrodes on SEEG in the insular cortex and SII regions were involved earliest at the onset of PSS, with early electrographic propagation to the opercular regions of SI, and later to the upper portions of SI and to CG. Perceptions of ictal pain did not appear to correlate in a time-locked manner in those regions of reported propagation. Furthermore, pain was consistently reproduced during ESM of the insula or SII regions but not by stimulating SI directly.

Cortical mapping studies utilizing ESM appear to demonstrate that pain is not produced in the SI, SSMA, or CG. An extensive study reporting responses to 4160 cortical electrical stimulations of the cortical surfaces demonstrated pain in 60/558 or 11% of triggered responses to stimulation in the SII and insular areas, and no pain or unpleasant sensations in any other regions [34]. The operculo-insular cortex has also been subjected to thermal or noxious laser stimulation experimentally, with responses elicited similar to ESM [32].

Functional neuroimaging studies also support increased bilateral operculo-insular activity corresponding to discrimination of stimuli above a painful threshold and pain of progressive intensity [33]. While some neurons responding to nociceptive stimuli appear to be sparsely present in the SI region, functional neuroimaging and ESM studies suggest it is primarily involved with tactile qualitative and localizing functions, and less so specifically with pain perception [32, 35].

It is likely then that perceptions of somatosensory pain are due to ictal involvement of the insula and SII parietal operculum, and less so from the parietal region, though this does not necessarily imply seizures originating in those locations or direct anatomic lesions, as symptoms may manifest upon propagation to these regions from other areas. Thus, seizures with onset from other nearby locations, along the pain network, may spread to these regions and activate the perception of pain. This may account for some of the variability in the anatomic localization of PSS based on lesional data from neuroimaging or utilizing other methods such as non-invasive scalp EEG, lateral surface intracranial electrode recordings, and functional neuroimaging studies [27••].

Treatment

For cases refractory to AED therapy, successful surgical attempts to cure operculo-insular epilepsy have been reported, though this region is technically difficult to approach surgically and study invasively [27••, 36–38]. The perisylvian area is highly vascularized and surrounded by functional and potentially eloquent cortex. In one case series of operculo-insular cortectomies performed for epilepsy, 20 out of 25 patients or 80% achieved freedom from disabling seizures [39]. Most had cortectomies in the adjacent lobe, and the rate of postoperative neurological complications was relatively high at 76%, including mild to moderate contralateral paresis and language disruptions (in dominant hemispheric resections), with 2 patients notably experiencing altered contralateral thermal and pain sensation. However, most deficits were early, transient, and rarely long term. Lesions created by radiofrequency thermocoagulation have been performed at the time of SEEG via implanted depth electrodes [27••, 37]. At our own institution, we have used laser interstitial thermal therapy (LITT) in one posterior insular case involving PSS following confirmation of seizure onset by SEEG.

Abdominal Pain as a Symptom of Seizures

Description

Abdominal pain during seizures is rare with one study reporting ictal abdominal pain in only 2 patients out of 4736 PWE evaluated at a tertiary epilepsy center [2•]. Although many PWE may mention other abdominal sensations (such as epigastric rising) as a manifestation of their seizures, true abdominal pain is uncommon [40]. When it occurs ictally, the seizures usually last less than 10 min in duration and can sometimes cluster. The patient often describes having paroxysmal sharp sensations or colicky discomfort [41].

Abdominal pain is usually part of the larger diagnosis of abdominal epilepsy, a condition that can present with paroxysmal episodes of non-specific abdominal complaints with definite corresponding EEG abnormalities and a positive response to the use of AEDs [42, 43]. A 2005 review, looking at 36 cases of abdominal epilepsy found that the most common symptoms in abdominal epilepsy were abdominal pain, nausea, vomiting, lethargy, and paroxysmal confusion [44].

Localization

The most common interictal scalp EEG abnormalities in abdominal epilepsy are epileptic discharges over the temporal

lobes (unilateral or bilateral), with case reports showing ictal abnormalities localizing to the temporal lobes [40, 45, 46]. Although not completely understood, it is believed that neuroexcitation of the temporal lobe may involve the amygdala which transmits to the gastrointestinal tract via the dorsal motor nucleus of the vagus nerve [47]. Less commonly, parietal seizure foci have been documented as well [18, 47]. As a common mimic of temporal or fronto-parietal epilepsy, the insula and operculum should also be considered as a possible source of these sensations, for similar reasons as described above in the section covering PSS [38]. In the largest published study of insular ESM, visceral sensations of abdominal heaviness and a constricting sensation were noted in several insular regions [48•].

Treatment

Patients with abdominal pain and non-specific abdominal complaints, especially with other neurologic symptoms such as confusion present during or after the episodes, should work up for abdominal epilepsy after other common etiologies are excluded in order to proceed with treatment. Studies prior to the development of the second generation AEDs showed that phenobarbital, phenytoin, carbamazepine, valproic acid, and phenytoin were effective in the treatment of abdominal epilepsy and pain [49]. A 2012 study of abdominal epilepsy in a pediatric population found that 92% of children responded well to the use of oxcarbazepine [42]. If medications are not successful, a surgical workup may be pursued, depending on the severity of symptoms and ability to identify a seizure focus. There appear to be only rare published reports on resective surgical treatments specifically for the condition of abdominal epilepsy. A case of seizures with abdominal pain cured by amygdala-hippocampectomy has been described [50]. Another recent article did indicate response of ictal abdominal pain to vagal nerve stimulation [51].

Conclusions

Pain as a presenting feature of seizures is a striking but unusual diagnostic entity. The cortical localization of epileptic somatosensory pain gives fascinating insights into the cortical network involved with pain processing. Headaches associated with seizures reveal some of the overlapping physiologic mechanisms between these two entities. Patients may remain misdiagnosed when symptoms occur in isolation from other neurological symptoms of seizures, and delays to correct evaluation and initiating treatment may occur. Video EEG monitoring is considered the gold-standard diagnostic evaluation, though focal sensory seizures with preserved awareness may occur without clear ictal electrographic correlate by scalp recordings. The presence of neuroradiographic lesions, stereotypic events, and response to AED treatment may be helpful determining factors, though awareness of this clinical entity is essential for diagnosis.

Compliance with Ethics Guidelines

Conflict of Interest The authors declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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