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EEG abnormalities as a biomarker for cognitive comorbidities in pharmacoresistant epilepsy

Gregory L. Holmes

Department of Neurology, Neuroscience Center at Dartmouth, Geisel School of Medicine at Dartmouth, Hanover, New Hampshire, U.S.A

Summary

Cognitive impairment is a common and often devastating comorbidity of pharmacoresistent epilepsy. The cognitive comorbidity can be both chronic, primarily due to the underlying etiology of the epilepsy, and dynamic or evolving because of recurrent seizures or interictal spikes. There is now considerable evidence that interictal spikes can contribute to cognitive impairment. Interictal spikes in both rodents and humans result in transient impairment of memory retrieval, whereas in immature animals, interictal spikes can result in long-term adverse effects on brain development. Interictal spikes therefore contribute to the cognitive impairment in the pharmacoresistant epilepsies. Effective treatment of pharmacoresistant epilepsy needs to target not only the overt seizures but interictal electroencephalography (EEG) abnormalities as well.

Keywords

Interictal spikes; Cognition; Learning; Memory

Of the comorbidities associated with epilepsy, cognitive abnormalities are the most common and severe (Hermann et al., 2008; Austin, 2009). Mental retardation, learning disabilities, and memory impairment are increased in people with epilepsy (Pellock, 2004; Hermann et al., 2008). Individuals with pharmacoresistant epilepsy are at particular high risk for cognitive impairment, particularly when the seizures begin during early childhood (Berg et al., 2012). The consequences of such comorbidities greatly diminish the quality of life in individuals with epilepsy, and many people with epilepsy, and their families, consider the cognitive and behavioral consequences of seizures to be at least as troubling as the seizures themselves.

When considering the pathophysiologic mechanisms of the cognitive consequences of epilepsy, it is helpful to distinguish between impairments that are permanent, that is, caused by etiology of the epilepsy and those that are dynamic, that is, progressive or transient (Kleen et al., 2012). The etiology of the epilepsy is the primary determinant of the

Address correspondence to Gregory L. Holmes, Neuroscience Center at Dartmouth, Geisel School of Medicine at Dartmouth, One Medical Center Drive, Lebanon, NH 03756, U.S.A. Gregory.L.Holmes@dartmouth.edu.

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permanent deficits. Etiologies such as trauma, hypoxia-ischemia insults, genetic disorders, mesial temporal sclerosis, and malformations of cortical development cause both the seizures and cognitive disturbances.

The second type of impairment is dynamic in the sense that the deficits are either happening in stages or transiently affecting the patients. These cognitive and behavioral deficits can occur as a result of the seizures, interictal epileptiform abnormalities, or antiepileptic drug therapy. This review examines one of the dynamic causes of cognitive impairment: interictal spikes (IIS). However, it is important to recognize that in the clinic multiple dynamic effects may combine with permanent ones to contribute to the individual's cognitive problems.

Cognitive Comorbidities and Interictal Spikes

IIS can produce brief disturbances in neural processing, resulting in a phenomenon called transitory cognitive impairment (Binnie, 2003). However, they rarely produce overt cognitive or behavioral disturbances. In a seminal study, Aarts et al. (1984) noted that IIS can briefly disrupt neural processes, affecting function within the brain region where they occur. The authors analyzed the effect of IIS on verbal or nonverbal short-term memory in patients with epilepsy but without overt clinical manifestations during these discharges, thus targeting the so-called "subclinical" manifestations of IIS. In right-handed individuals the authors reported that right-hemisphere IIS were associated with errors in a nonverbal task, whereas left-hemisphere IIS resulted mainly in errors in verbal tasks. Electroencephalography (EEG) discharges interfered mainly when they occurred simultaneously with the presentation of the stimulus, corresponding with the encoding phase of the task. Shewmon & Erwin (1988a,b,c, 1989) in a series of carefully performed studies further localized the effect, noting that occipital IIS could disrupt visual perception. IIS in the occipital region caused transitory deficits with stimuli presented in the contralateral visual field. Deficits were most pronounced when they occurred during the slow wave following the IIS.

Kleen et al. (2010) used a within-subject analysis to analyze how IIS might independently affect multiple processes in the hippocampus. The investigators studied rats that developed chronic IIS following intrahippocampal pilocarpine in a hippocampal-dependent operant behavior task: the delayed-match-to-sample. Hippocampal IIS that occurred during memory retrieval strongly impaired performance. However, IIS that occurred during memory encoding or memory maintenance did not affect performance in those trials. IIS were most dysfunctional when occurring when hippocampal function was critical, similar to human studies showing that cortical spikes are most disruptive when occurring during the active engagement of neurons involved in performing the task.

Single cell firing patterns have been investigated following IIS in rodents. There is a sustained reduction of action potentials in the hippocampus for up to 2 s following a local IIS. Furthermore, when occurring in flurries, IIS can reduce action potential firing for up to 6 s (Zhou et al., 2007). The response to IIS is cell dependent; IIS result in decreases in action potential firing after the IIS among interneurons but not pyramidal (place) cells. The widespread inhibitory wave immediately after IIS can also reduce the power of gamma

oscillations and other oscillatory signals in the hippocampus (Urrestarazu et al., 2006). Because oscillations are closely coupled with ongoing learning and memory functions, this disruption in oscillations likely contributes to cognitive deficits (Halasz et al., 2005; Kleen et al., 2010).

In a study of 10 adult patients with intracranial depth electrodes implanted bilaterally into the hippocampi for preoperative seizure localization, Kleen et al. (2013) recorded 2,070 total trials of the Sternberg test, a shortterm memory task. As with the rodent study, memory processing was categorized into encoding, maintenance, and retrieval. Hippocampal IIS occurring in the memory retrieval period decreased the likelihood of a correct response when they were contralateral to the seizure focus or bilateral. Bilateral IIS during the memory maintenance period had a similar effect, whereas IIS during encoding had no effect. The results strengthen the view that IIS contribute to cognitive impairment in epilepsy depending upon when and where they occur. The results of this study confirmed an earlier study by Krauss et al. (1997) who found declines in working memory due to IIS.

There are lessons about interictal abnormalities learned from both the animal and human studies. First, in order to disrupt a particular process, the IIS must incorporate the neural circuits involved in that process, stressing the importance of matching the affected neural substrate with a cognitive test that assesses its intrinsic function. Second, the IIS must occur at a particular moment in cognitive processing such that the process is vulnerable to disruption. Third, the deficits elicited by the IIS can be subtle and short lived.

In addition to causing transitory cognitive impairment, IIS during early brain development may have long-term adverse effects on the developing neural circuits. In some interesting studies of the effects of IIS on network development, IIS were elicited by either penicillin (Baumbach & Chow, 1981; Crabtree et al., 1981) or bicuculline (Campbell et al., 1984; Ostrach et al., 1984) through focal application on the striate cortex of rabbits. IIS were elicited for 6–12 h following each drug application, which was given daily from postnatal (P) day 8–9 to up to P24–30. Despite frequent IIS, none of the rabbits had behavioral seizures. In single-unit recordings from the lateral geniculate nucleus, superior colliculus, and occipital cortex ipsilateral to the hemisphere with IIS, there was an abnormal distribution of receptive field types, whereas normal recording was found from the contralateral hemisphere. Remarkably, this finding was age dependent. Rabbits with similarly induced IIS during adulthood had normal development of cells, highlighting an additional vulnerability of critical developmental periods to cumulative IIS effects over time.

IIS have also been elicited in young rats with flurothyl, an inhaled convulsant (Khan et al., 2010). Rat pups were given a low dose of flurothyl for 4 h for a period of 10 days during continuous EEG monitoring. Rats developed IIS without seizures, whereas age-matched controls under similar testing conditions showed few IIS. When rats were tested as adults, there was impairment in reference memory in the probe test of the Morris water maze, reference memory impairment in the four-trial radial-arm water maze, and impaired long-term potentiation. Early life IIS also resulted in impaired new cell formation and decreased cell counts in the hippocampus, indicating a potential mechanism in which IIS during

development can produce cumulative lasting effects in addition to any dynamic disruptions. It appears from these data that IIS, like seizures, during brain development have a cumulative effect on cognitive function.

Summary

There is now clear evidence that IIS in animals and humans can result in cognitive impairment. The degree to which IIS contributes to cognitive impairment in most individuals with cognitive impairment is likely to be modest, particularly in comparison to the etiology of the epilepsy, antiepileptic drugs, and the seizures themselves. However, in patients with frequent IIS occurring 24 h/day, the IIS themselves may play a significant role in cognitive function. In young children where activity-driven mechanism drives neuronal connectivity, IIS may have persistent adverse effects on brain development that extend beyond the time of the IIS. Future therapeutics need to consider not only the overt seizures but the EEG abnormalities as well.

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