

Relationships Between Interictal Spiking and Seizures: Human and Experimental Evidence

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ABSTRACT: Epileptic seizures of focal origin often occur unpredictably as do interictal spikes. It is often assumed that spikes increase prior to seizures of focal origin and that antiepileptic medication affects spikes and seizures in a parallel fashion. We review evidence that this assumption is invalid and that there is a clear dissociation between spikes and seizures: increases in spiking before seizures have not been clearly documented; decreases in antiepileptic medication do not result directly in increased spiking; seizures are often followed by long-lasting increases in spiking; finally, seizures are no more likely when spikes are frequent than when spikes are rare. It therefore appears that spikes and seizures are two quite distinct phenomena, both originating in the epileptic focus but varying over time differently from what is most often believed.

RÉSUMÉ: Relations entre les pointes intercritiques et les crises épileptiques: données humaines et expérimentales. Les crises épileptiques d'origine focale sont le plus souvent imprévisibles, comme le sont les pointes intercritiques même si ces dernières sont plus fréquentes. On suppose souvent que les pointes intercritiques deviennent plus fréquentes avant les crises, et que les médicaments antiépileptiques modifient les crises et les pointes de manière semblable. En fait, les résultats prouvent plutôt une forte dissociation entre pointes et crises: une augmentation pré-ictale des pointes n'a jamais été établie clairement; la réduction de la médication antiépileptique n'a pas pour effet direct une augmentation des pointes; les crises sont souvent suivies d'une augmentation de l'activité intercritique; enfin, la probabilité d'apparition d'une crise ne dépend pas de l'intensité de l'activité intercritique. Nous en concluons que pointes et crises sont deux phénomènes très distincts, ayant tous deux leur origine dans le foyer épileptique mais fluctuant au cours du temps d'une manière différente de ce qu'on pense habituellement.

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In almost all patients with focal epilepsy, interictal epileptiform activity can be recorded from the focus and sometimes from other brain regions. In fact the localization of the focus originates in part from that of interictal spikes. I will not address the spatial relationships between these two phenomena in this paper but rather the question of how spikes and seizures are related over time. It is often assumed that spikes and seizures have a parallel time course such that when spikes become more frequent, seizures are more likely and if spikes are rare or absent, seizures are less likely. Following this logic, interictal EEGs are sometimes recorded in patients who are seizure-free to help decide whether antiepileptic medication should be discontinued: the absence of spikes then weighs in favour of discontinuation. Similarly, it is frequently believed that interictal spiking can be activated by reducing medication (administered for reduction of seizures).

I would like to provide evidence for relationships between spikes and seizures which are quite different; the view of the

spike as a "mini-seizure" which evolves in the same direction as seizures is not supported by this evidence. Rather, I will provide evidence for a counter-intuitive hypothesis: that fluctuations of spiking activity over time are in large part determined by the occurrence of seizures, that most antiepileptic medications have little direct effect on spiking and that the rate of spiking is more a reflection of past seizures than an indication of the likelihood of impending seizures.

Spiking activity before seizures

It is often said that spiking activity increases before seizures and sometimes it is said that it decreases before seizures. In fact I could find no well-controlled study that establishes these facts either in experimental models of epilepsy or in patients. It is important to define the time scale being considered: changes "before" a seizure do not mean the few seconds preceding the seizure but rather the minutes, hours or even days that precede a seizure. It is indeed not infrequent that spiking activity increases,

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or stops, in the 5, 10 or 20 s before a seizure discharge, but it can be argued that these changes in spiking constitute the seizure onset itself. Lange et al.¹ examined changes in spiking rate and spatial distribution in the 20 min preceding temporal lobe seizures; they found no systematic change in rate (increase or decrease) but a tendency for spikes to appear in approximate synchrony over wider regions during that time than during earlier 20-min periods. The possibility that this was due to drowsiness was not excluded. In a study of changes in spiking preceding and following seizures² we also found no specific change in rate prior to seizure occurrence (Figure 1).

In the penicillin model of focal epilepsy, subtle changes in spiking patterns have been observed prior to seizures.^{3,4} In the kindling model, spiking becomes more frequent as the kindling process evolves; pre-ictal changes can of course not be studied for the usual stimulus-triggered seizures. Wada et al.⁵ and Pinel and Rovner⁶ claim that spiking increases prior to the appearance of spontaneous seizures but they did not monitor the animals' EEG continuously and we will argue that the increase they observed could be post-ictal. In the few cases where the EEG was monitored continuously and spontaneous seizures took place in kindled cats, we saw no change in spiking rate prior to the seizures.⁷ From these data we conclude that no systematic changes in spiking activity have been demonstrated in the minutes or hours preceding seizures.

Spiking activity after seizures

In a comprehensive study of the factors related to the presence or absence of interictal activity in the EEGs of epileptic patients, Ajmone-Marsan and Zivin found that very few of the factors they considered (duration of epilepsy, frequency of seizures, type of medication) were predictive of the presence of spikes.⁸ One factor, however, that showed some correlation with spiking was the presence of seizures in the 2 days preceding the recording. Ajmone-Marsan and Zivin give no interpretation for this finding, but a post-ictal increase in spiking could be postulated.

We have investigated the relationship between spiking and seizures during pre-surgical long-term monitoring of epileptic patients. In this study computerized long-term monitoring methods,⁹ which were able to quantify spiking rates over long periods of time¹⁰ provided an ideal situation for recognizing changes in spiking patterns before and after seizures. One major complicating factor is that antiepileptic medication is reduced gradually during pre-surgical evaluation to precipitate the occurrence of seizures. Since this confounding factor cannot be assumed to have the same effect on spikes and seizures it was eliminated by concentrating on patients or parts of monitoring sessions in which medication was absent or stable.

During these selected times there was no change in spiking rates prior to seizures. In contrast a most remarkable change took place after seizures: spiking rate increased immediately after many seizures and lasted from a few hours to 1 or 2 days.² The increased spiking could even last longer after multiple generalized seizures. The increase was not seen after all seizures: when studying patients with scalp electrodes increases were seen mostly after secondarily generalized seizures and rarely after partial seizures; when studying patients with intracerebral electrodes, increases were also seen after many partial seizures.

In that study,² however, we could not exclude the possibility that patients were more drowsy or slept more post-ictally than

pre-ictally and that the post-ictal increase in spiking was in fact due to an increase in slow wave sleep, which is known to activate spiking.¹¹ To eliminate this confounding variable, another study was undertaken¹² in which spiking rates were measured only while we ensured that the patient was awake. Again spiking rates increased only after a seizure, thereby allowing post-ictal increases in spiking to be attributed directly to the seizures. Furthermore, we established that spiking increases were not paralleled by changes in EEG background and were thus a phenomenon distinct from the well-known post-ictal slow waves.

Post-ictal increases in spiking rates were confirmed recently by Katz et al.¹³ in patients with intracerebral electrodes.

This post-ictal increase in spiking has also been found in fully kindled cats;⁷ after a single secondarily generalized seizure, the EEG showed a suppression of spiking during 3 to 5 hours followed by a large increase in spiking, taking 24 to 48 hours to return to baseline. After 10 consecutive days of daily seizures spiking activity took approximately one week to return to pre-seizure levels. These findings were confirmed in an independent set of experiments¹⁴ and by Leung.¹⁵

Antiepileptic medication and spiking activity

It is worth noting that in the study of Ajmone-Marsan and Zivin,⁸ the presence or absence of antiepileptic drugs (AEDs) was not a factor influencing the probability of seeing spikes in the EEG. In a review on antiepileptic drugs and the EEG, Duncan¹⁶ concluded that there is no demonstrated relationship between levels or effectiveness of AEDs and isolated spikes (bursts of widespread spike and wave activity are quite different in this respect, responding to AEDs much like seizures). Van Wieringen et al. reached a similar conclusion.¹⁷

Almost all studies examining relationships between EEG and AEDs proceed by recording the EEG in a baseline condition and then recording later (days, weeks or months) when the levels of AEDs are changed. We concur with Duncan;¹⁶ although AEDs have definite effects on seizures, we would like to argue that many AEDs have no direct effect on spiking activity even when they are effective against seizures.

When AEDs are reduced during pre-surgical evaluation of epileptic patients, we have found that spiking rates do not change, unless seizures occur.^{2,12} Figure 1 illustrates such a situation and Figure 2 illustrates a case where no seizure took place during a long period; despite discontinuation of carbamazepine, the spiking rate remained remarkably stable.

Interpreting these results, together with those given above regarding post-ictal increases in spiking, it is easy to understand why it is often believed that decreasing AEDs results in increased spiking: reduction of AEDs result in seizure occurrence, which in turn results in increased spiking.

Another type of evidence on the effect of AEDs on spiking comes from chronic animal experiments. Administration of carbamazepine to fully kindled cats does not decrease spiking rate; in fact it results sometimes in an increase in this rate¹⁴ despite the well established effect that carbamazepine has on kindled seizures. So far at least, there is no evidence that AEDs have a specific suppression action on spiking activity in the kindling model.

We do not review the vast literature on the effect of AEDs in acute models of epilepsy. Most studies do not address the question

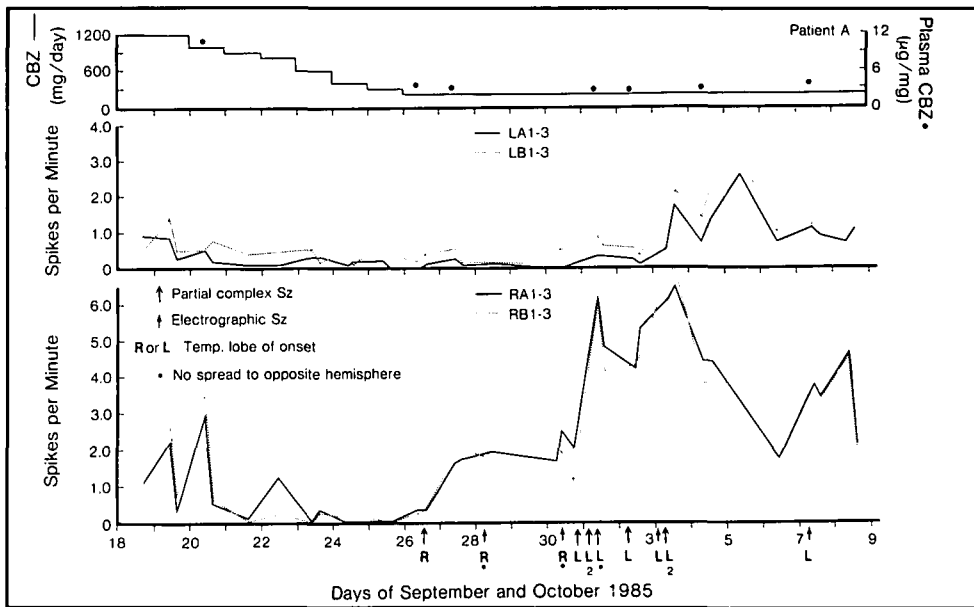


Figure 1 — Fluctuations in interictal spiking in a patient with intracerebral electrodes. Top graph indicates dosage and plasma level of carbamazepine (CBZ). Middle graph shows rate of interictal spiking in deep structures of left temporal lobe: amygdala (LA1-3), anterior hippocampus (LB1-3). Bottom graph shows rate of interictal spiking in homologous sites of right temporal lobe. Each point represents average spiking rate during a 15 min EEG sample. Since samples were taken at different time intervals, points are not equally spaced. Arrows indicate seizure occurrence: small arrows represent electrographic seizures without clinical accompaniments and standard arrows represent partial complex seizures. When more than one seizure occurred within a short time interval, the number of seizures is indicated below the arrow. Increase in spiking starts on the right hemisphere after right-onset seizures and in the left hemisphere after left-onset seizures (from reference 12).

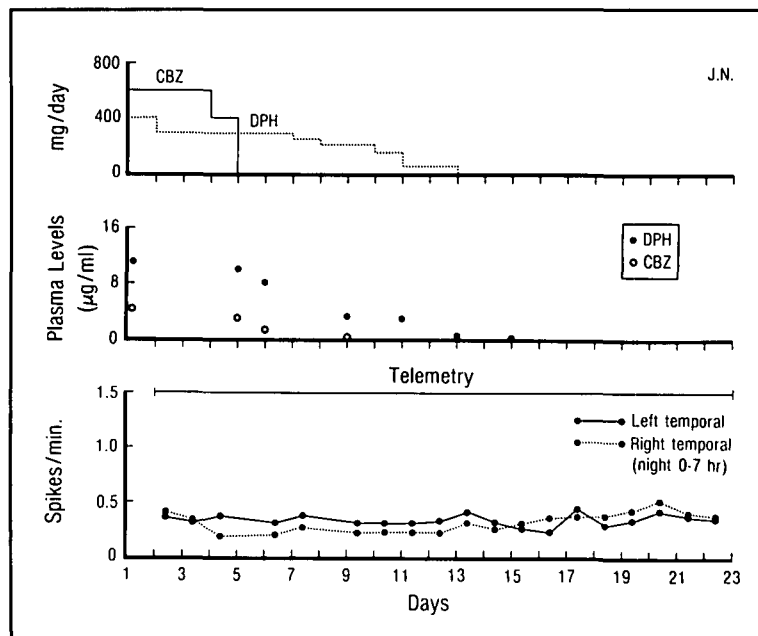


Figure 2 — Upper graph is medication dosage. Middle graph represents plasma levels and lower graph shows spiking rate in a patient with intracerebral electrodes. As antiepileptic medication decreases from "therapeutic" levels to zero, there is no change in interictal activity. Note that no seizure took place (from reference 2).

of differences between ictal and interictal activity. In a study that addresses this question, however, it was found that it was possible to block spikes without blocking seizure discharges and vice versa.¹⁸ The authors conclude that in their model, focal seizures and interictal spikes arise from different mechanisms: the former can be initiated by non-synaptic interactions while the later requires chemical synaptic transmission.

It should be noted that we have reviewed only evidence for the oral administration of AEDs. It has been shown that intravenous injection of phenytoin results in reduced spiking,¹⁹ as does the injection of diazepam.²⁰ There is no explanation for the discrepancy between systemic and intravenous administration. Finally, we did not discuss generalized epilepsy and generalized EEG patterns such as spike and wave: the distinction between ictal and interictal patterns is less clear and it seems that medication effective against generalized seizures also affects generalized spike and wave. The relationships between ictal and interictal phenomena have not been systematically examined in generalized epilepsy.

CONCLUSION

When examining relationships between interictal and ictal activity in focal human epilepsy, one cannot escape the issue of antiepileptic medication. However, to properly assess the effect of AEDs and the temporal relationships among drugs, spikes and seizures it is critical to record EEGs continuously to assess changes in spiking before and after seizures, since one must always know when seizures take place.

We have tried to demonstrate that there is no solid evidence for a change, either increase or decrease, in spiking rates in the hours or minutes preceding seizures. On the other hand, there is strong evidence for a frequent post-ictal increase in spiking, lasting from a few hours to a few days. Finally, antiepileptic medication which is effective against focal seizures appears to have no direct effect on spiking. Changes in spiking that are often seen after changes in medication are more likely mediated by the occurrence or disappearance of seizures, since seizures affect spiking.

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