

Status Epilepticus and Periictal Imaging

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Summary: Peri- and postictal changes on both anatomic and functional imaging examinations have been recognized for many years. With the wide availability of magnetic resonance imaging and positron emission tomography, a growing range of recognized acute imaging findings have been described. Periictal and postictal findings can be classified as either local or remote, with respect to the site of maximal ictal EEG abnormality. Although many of the findings described are reversible, the factors that determine whether findings will resolve are incompletely un-

derstood. This article considers the range of findings that have been described, places them into the context of known or hypothesized pathophysiologic mechanisms, and considers their clinical significance. A framework is proposed for considering the relation between ictal duration and severity, the characteristics of imaging abnormalities, and the mechanism of their underlying pathophysiology. **Key Words:** MRI—DWI—ADC—Diaschisis—PET—SPECT.

Periictal changes on anatomic and functional imaging studies have been recognized by clinicians since the early days of the computed tomography (CT) scan era (1). Patients with focal seizures were occasionally found to have effacement of gyral markings and diffuse patchy contrast enhancement on CT, usually colocalized with the presumed source of the ictal activity, and sometimes associated with apparent Todd's paralysis. These findings, which were sometimes mistakenly interpreted as evidence of an underlying brain tumor, typically resolved over hours or days, often to the embarrassment of the admitting physician. With the advent of [¹⁸F]fluorodeoxyglucose positron emission tomography (FDG-PET) scanning, occasional studies demonstrated hypermetabolism of glucose in patients who had fortuitous focal seizures during the period of tracer uptake (Fig. 1A). In some patients, repeated studies obtained during interictal periods demonstrated local hypometabolism reflecting the disordered function of neuronal networks in the region of the epileptic focus. More recently, the deliberate effort to obtain periictal imaging by using [⁹⁹Tc]-hexamethyl-propyleneamine-oxime (⁹⁹Tc-HMPAO) as a marker of local perfusion during seizures [ictal single-photon emission CT (SPECT)] has gained acceptance as a localizing tool in the presurgical evaluation of patients with refractory seizures (Fig. 1B) (2) [See also articles by Cascino (pp. 32–34) and Van Paesschen (pp. 35–40) in this volume.]

With the widespread availability of magnetic resonance imaging (MRI), sometimes in emergency department settings, a growing range of periictal imaging findings have been described. In this article, I outline an approach to classifying these findings, and I consider their clinical significance and potential pathophysiologic basis. For this discussion, we consider findings on imaging studies that arise during or immediately after seizures, and we refer to this period as “periictal.”

CLASSIFICATION OF PERIICTAL IMAGING FINDINGS

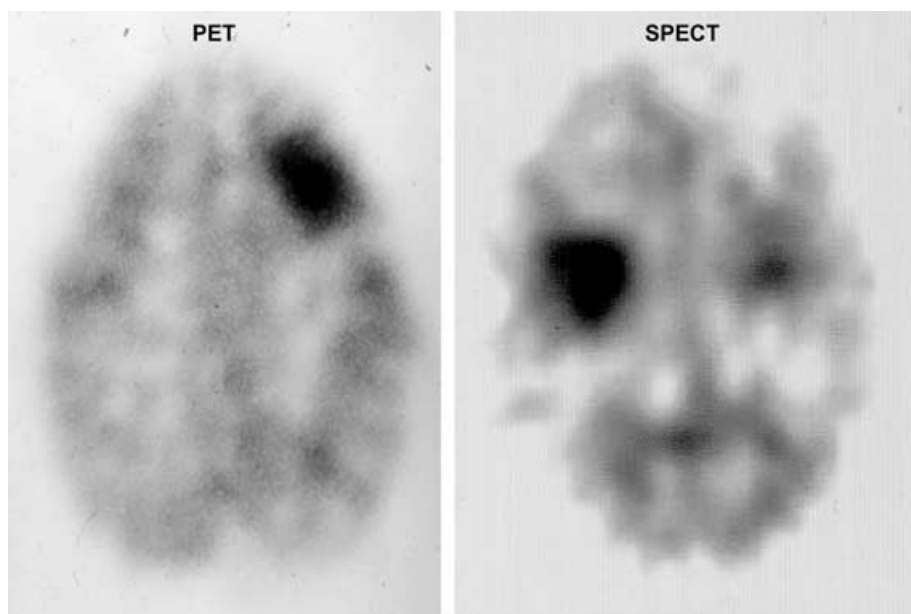
Periictal imaging changes may occur in the region of the epileptic discharge (local) or in distant structures (remote). Some of the findings that have been described are listed in Table 1. Each of these findings may be reversible or irreversible.

Remote periictal findings

The pathophysiologic basis of lesions that occur remote from the site of ictal activity is not understood. Presumably ipsilateral diencephalic and contralateral cerebellar lesions arise as a consequence of abnormal activity in those structures, driven by the epileptic activity. Crossed cerebellar diaschisis, observed in ischemia, may be a striking finding in status epilepticus (Fig. 2). Transient lesions of the splenium (Fig. 3) also may reflect abnormal activity in white matter tracts driven by the epileptic focus, but neither the mechanism nor the precise nature of the white matter change responsible for the increased T₂ signal and restricted diffusion in the splenium is understood. One

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FIG. 1. Ictal [¹⁸F]fluorodeoxyglucose (FDG)-positron emission tomography (PET) and [⁹⁹Tc]-hexamethyl-propyleneamine-oxime (HMPAO)-single-photon emission computed tomography (SPECT) images. **A:** ¹⁸FDG-PET image obtained from a 4-month-old infant subsequently found to have a focal cortical dysplasia in the region defined by glucose hypermetabolism. **B:** ⁹⁹Tc-HMPAO-SPECT image from a 24-year-old woman with partial epilepsy of previously uncertain origin. Tracer was injected 10 s after initial behavioral change. Scalp EEG recordings were completely obscured by muscle and movement artifact.



study suggested that corpus callosum lesions were due to anticonvulsant drug (AED) toxicity (3), but this seems unlikely, given the large number of patients taking AEDs who undergo MRI. Moreover, several cases have been reported in patients off AEDs who had flurries of seizures (4,5). Polster et al. (6) suggested that drug withdrawal might underlie this phenomenon, but their argument rested on the notion that the splenium lesion was vasogenic edema. Our finding that the lesion demonstrates a decreased apparent diffusion coefficient (ADC) is not consistent with their hypothesis, and rather supports the idea that in most cases, the lesion is likely to be related to the ictal activity per se (4).

Microvacuolization of the myelin is one pathologic substrate that could account for both the increased T₂ signal, the decreased ADC, and the reversibility of the lesion that has been suggested. Interestingly, in our experience, several patients with splenial lesions, all of which have been reversible, have had bitemporal independent epileptic foci and associated psychiatric disease. It is tempting to speculate that acute dysfunction of interhemispheric connections may contribute to the pathophysiology of postictal psychiatric disturbances. Careful examination of

patients in the future with postictal psychosis may clarify this point. The syndrome of posterior reversible leukoencephalopathy (RPLE), described in patients with hypertension, eclampsia, and sometimes in association with certain immunosuppressive drugs, is frequently associated with repeated seizures (7,8). Some patients with seizures, but without another obvious cause for RPLE,

TABLE 1. Classification of periictal imaging abnormalities

Local	Remote
Mass effect	Posterior leukoencephalopathy
Hippocampal swelling	Unilateral/bilateral diencephalic lesions
Focal cortical lesions	Splenium abnormalities
Migratory lesions	Cerebellar diaschisis
Blood-brain barrier breakdown	
Increased vessel caliber/flow	

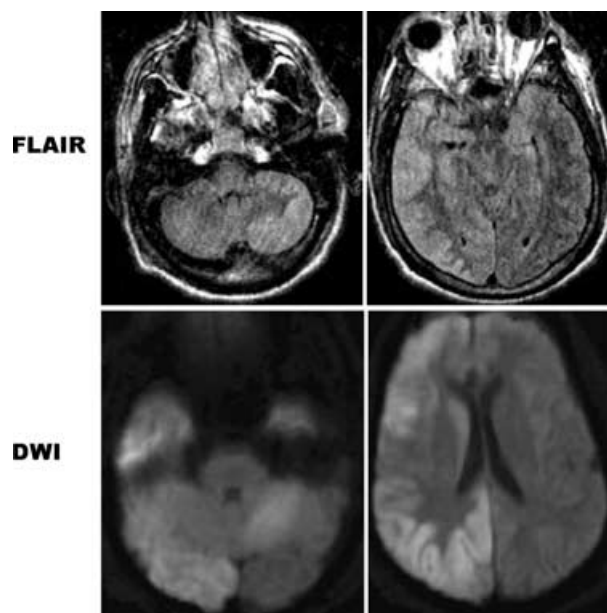


FIG. 2. Crossed cerebellar diaschisis. Images obtained from a 38-year-old patient with recurrent right hemispheric seizures. **Upper panels:** Abnormal signal on fluid-attenuated inversion recovery images in the ipsilateral cortical ribbon and in the contralateral cerebellar hemisphere. **Lower panels:** Reduced diffusion on diffusion-weighted images in corresponding regions.

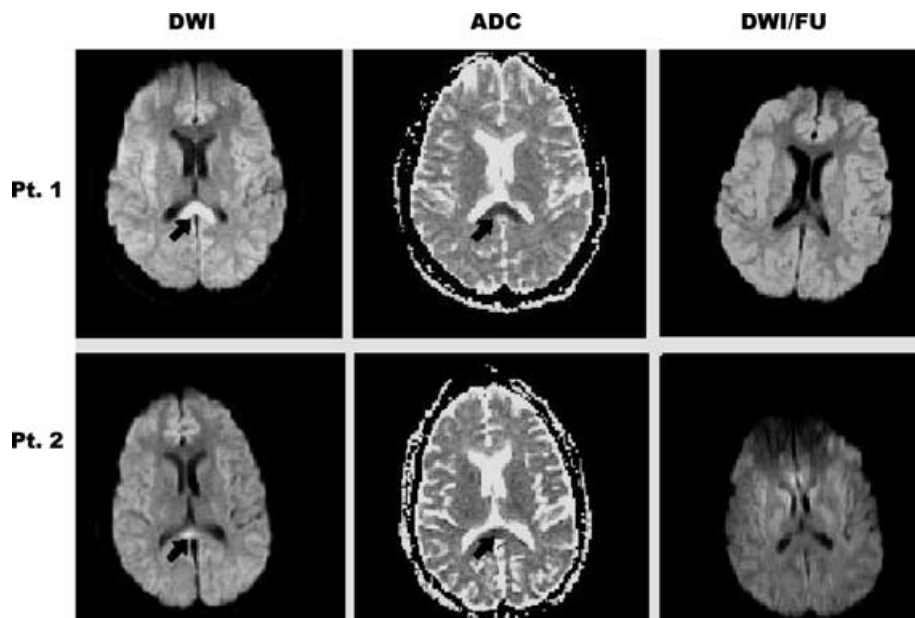


FIG. 3. Transient diffusion-weighted imaging changes in the splenium after seizures. Representative images from two patients (**upper and lower panels**) demonstrate restricted diffusion (**left**) with associated decreased apparent diffusion coefficients (**center**) that resolved in 4–6 weeks (**right**). (Reproduced with permission from ref. 4.)

have been described, suggesting that seizures per se may contribute to the occurrence of this finding. This syndrome points out the difficulty of determining cause and effect with respect to seizures and imaging abnormalities, an exercise that should be undertaken with great caution.

Local periictal findings

It is, perhaps, conceptually easier to consider the pathophysiologic basis of local periictal imaging findings. These, which include T_2 , ADC, and vascular changes are seemingly related to increased neuronal activity and its associated metabolic and vascular responses. Local swelling of hippocampus has been described in children with prolonged febrile convulsions (9), and effacement of gyri in the region of epileptic discharge may be seen in all age groups (10). Increased T_2 signal intensity, indicating an increase in brain water, occurs in areas of cortex and subcortical white matter in association with some prolonged or intense seizures (11). Many of these lesions show restricted diffusion [bright on diffusion-weighted imaging (DWI), dark on ADC maps], supporting the idea that they represent cytotoxic rather than vasogenic edema; however, these lesions are reversible, at least initially, indicating that cell death is not an inevitable sequela (Fig. 4). A particularly interesting finding is the occasional occurrence of migratory T_2 and DWI lesions. In one such case, we witnessed evanescent lesions arising in widely separated areas of cortex, persisting for days to weeks, and then resolving (Fig. 5). By using coregistration of ^{18}F FDG-PET and MRI, we were able to demonstrate that lesions inevitably colocalized with regions of focal hyperme-

tabolism (Fig. 6), and these in turn corresponded to areas of maximal EEG abnormality. In this situation, it seems most likely that the lesions are the consequence of the epileptic activity, and not its cause. Magnetic resonance angiography studies in patients in status epilepticus may demonstrate increased flow-related enhancement, and this finding corresponds well to the observation of arterialization of venous blood reported by surgeons examining the cortex during provoked or spontaneous epileptic seizures

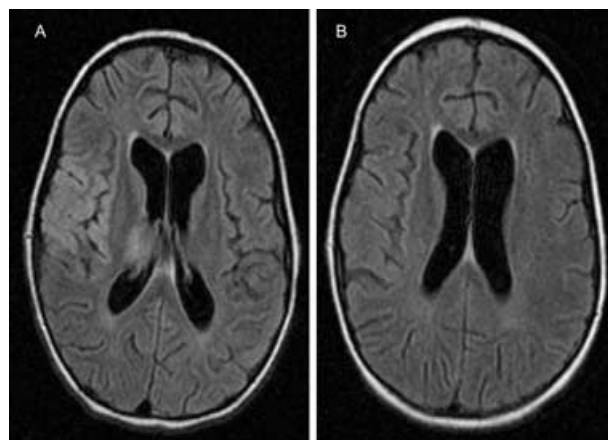


FIG. 4. Resolution of increased T_2 signal associated with focal status epilepticus after 7 days of pentobarbital (PTB) anesthesia. Patient was a 12-year-old girl seen 14 days before **left** scan, with epilepsy partialis continua arising from the right hemisphere. After 7 days of PTB anesthesia titrated to produce burst-suppression on continuous EEG monitoring, T_2 signal changes largely resolved (**right**). Images were obtained by using a fluid-attenuated inversion recovery protocol. (Adapted from ref. 4, with permission).

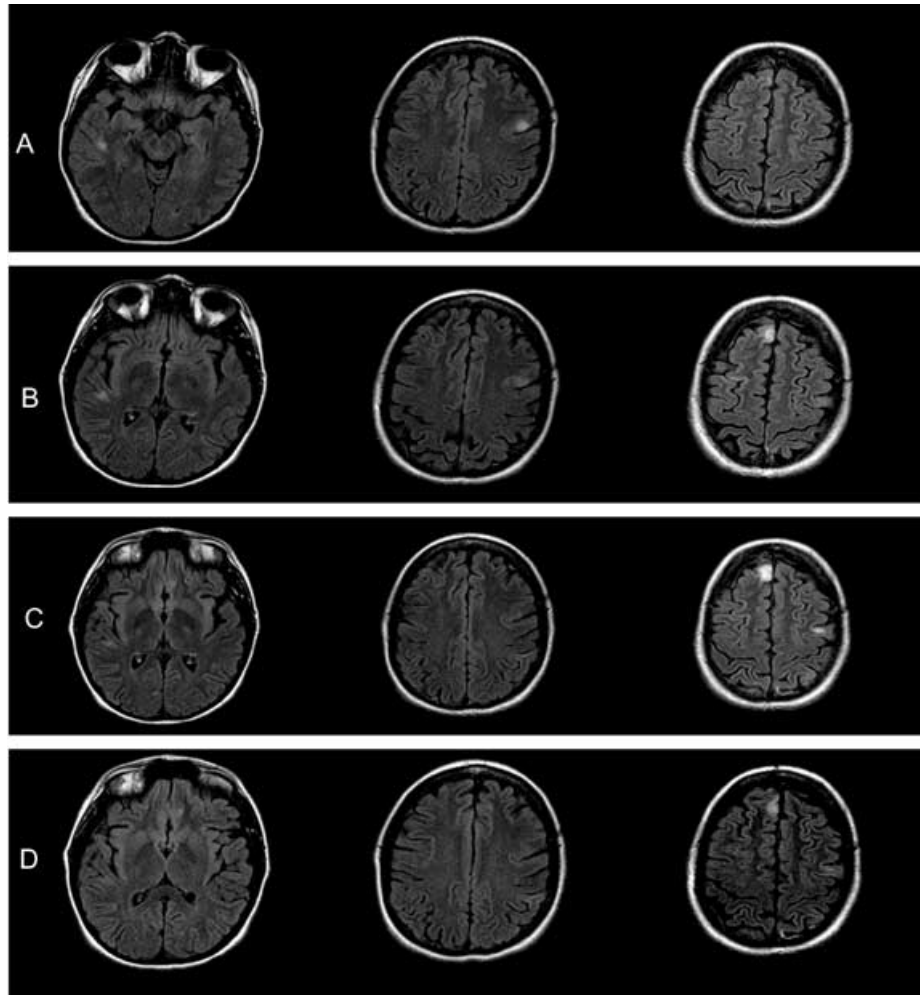


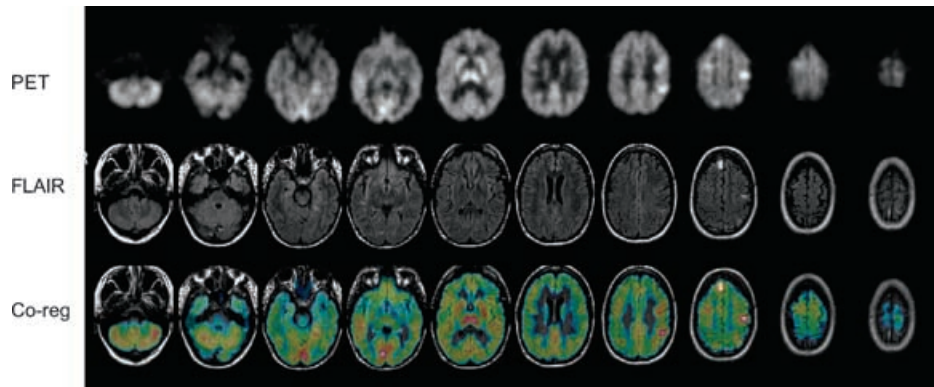
FIG. 5. Migratory periictal imaging changes. Fluid-attenuated inversion recovery images obtained at multiple levels at time of presentation (A), on day 14 (B), on day 28 (C), and on day 35 (D) from a 28-year-old woman with recurrent partial seizures associated with a mitochondrial disease.

(Fig. 7). Simultaneous SPECT studies in this circumstance may not demonstrate evidence of increased perfusion at the microvascular level, suggesting that some portion of the local increased bloodflow represents arteriovenous shunting.

Relation between T₂ and ADC findings

Diffusivity is an intrinsic property of tissue, and the ADC is independent of both T₁ and T₂ relaxation times. T₂ relaxation time is largely reflective of local brain water content. Whereas increased T₂ signal suggests edema

FIG. 6. Multimodal imaging with magnetic resonance imaging and positron emission tomography (PET). **Top:** [¹⁸F]fluorodeoxyglucose–PET images from patient described in Fig. 5, obtained on day 25, showing multiple focal areas of hypermetabolism. **Middle:** Fluid-attenuated inversion recovery (FLAIR) images obtained on day 28. **Bottom:** Coregistration showing colocalization of areas of hypermetabolism and areas with FLAIR abnormalities. EEG recording (not shown) demonstrated a similar localization of ictal activity involving right frontal pole and left central region.



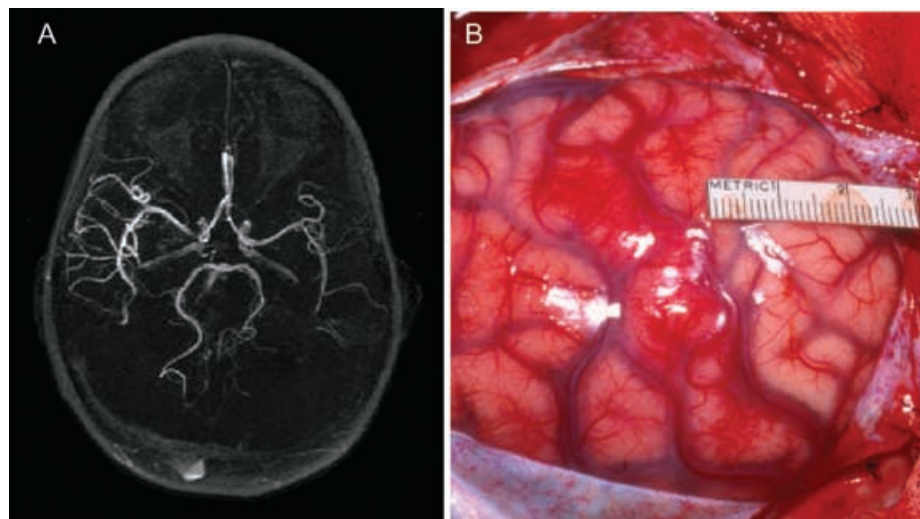


FIG. 7. Cortical hyperemia associated with increased flow-related enhancement in a patient in focal status epilepticus. Magnetic resonance angiogram showing dilatation of the right middle cerebral artery (MCA) branches presumably reflecting increased blood flow to the active cortex (A). Intraoperative photograph showing right motor strip exposed beneath the dura (B). Clinical description is as in the legend of Fig. 5. (Figure adapted from ref. 4 with permission).

or gliosis, restricted diffusion is usually associated with metabolic dysfunction or energy deficiency. Some of the hypothesized causes of restricted diffusion are listed in Table 2. Restricted diffusion has commonly been identified as a marker of irreversible ischemic injury, but recent studies suggest that in some situations, decreased diffusion associated with seizures is reversible without the subsequent appearance of tissue injury (12). The temporal relation between the appearance of restricted diffusion and T₂ signal change in association with seizures may be variable. Whereas in acute ischemia, DWI images reveal restricted diffusion before any abnormality of T₂ signal becomes apparent, in ongoing status epilepticus, DWI and T₂ signal changes appear to occur roughly synchronously. These differences in the timing of DWI and T₂ signal change suggests a difference in the underlying pathophysiology. Whereas in ischemia, early energy failure occurs, in ongoing status, activity-induced injury with cytotoxic edema may precede overt energy deficiency.

Variability in occurrence of periictal imaging changes

An important and unresolved issue is why local acute periictal changes on MRI occur in some but not all patients after focal seizures. The fact that such changes are sometimes first apparent days or weeks after the start of focal status (13, for example) suggests that a threshold of seizure duration and/or severity exists, below which

changes will not occur. Current knowledge does not allow us to predict with any degree of certainty where that threshold might lie, but in Fig. 8, I have drawn a conceptual diagram that attempts to relate imaging changes to perfusion and energy demand. An important concept illustrated in the figure by the divergence between the dotted and solid lines is that at some point, imaging changes become irreversible. It is important that, as with most threshold phenomena in biology, it is likely that differences between individuals exist in both when imaging findings will become apparent and when they will become irreversible. Some critical variables that might determine whether seizures in a specific individual are sufficient to trigger acute imaging changes are listed in Table 3.

CONCLUSIONS

Although there is increased recognition of acute periictal imaging changes in the clinical community, most reports are anecdotal, and few if any series exist. Interpretation of these findings therefore remains highly speculative. Nonetheless, the variety of findings that have been described and the occurrence of changes both locally and remotely with respect to the ictal zone suggest a number

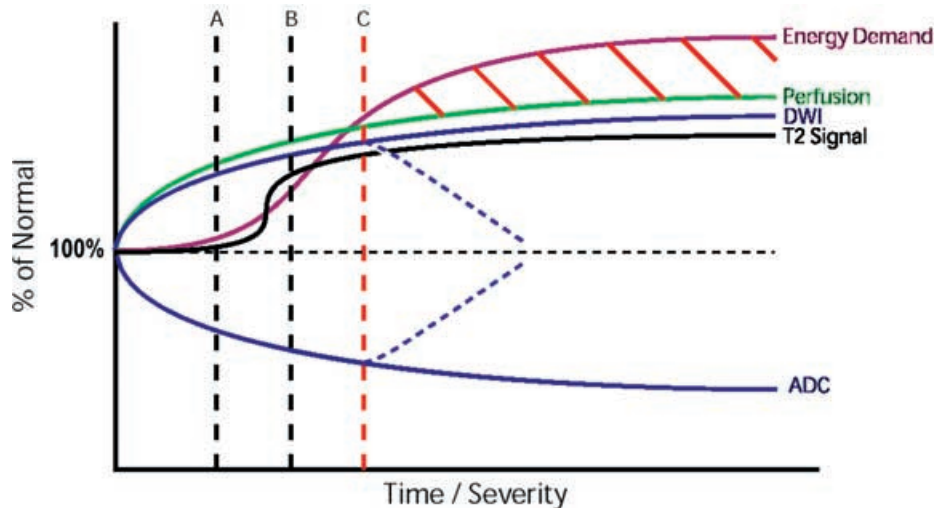
TABLE 2. Causes of restricted diffusion

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| <ul style="list-style-type: none"> • Na⁺-K⁺-adenosine triphosphatase (ATPase) pump failure • Cytotoxic edema • Increased intracellular viscosity due to cytoskeletal fragmentation • Increased tortuosity of intracellular space • Decreased extracellular volume |
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TABLE 3. Critical variables that may determine occurrence or severity of local periictal imaging changes

Seizure type/location
Duration/severity of ictal discharge
Host characteristics
Age
Preexisting conditions
Cardiovascular/metabolic reserve
Pharmacologic intervention

FIG. 8. Conceptual cartoon illustrating a possible relation between energy supply, energy demand, and observed periictal imaging changes. Red hatch marks, potential irreversibility due to energy deficit. Dotted blue lines, potential reversibility of diffusion-weighted imaging abnormalities before onset of unrecoverable energy deficit. **A–C:** Early, middle, and later stages of seizure severity/duration at which snapshot imaging findings might be predicted from the diagram.



of intriguing hypotheses and raise a variety of clinically relevant questions.

One hypothesis that can be tested in a prospective fashion is that the evolution of imaging changes, including the appearance of ADC decrease, T_2 increase, changes in flow-related enhancement, and occurrence of irreversibility correlate with the evolution of electrophysiologic findings in status epilepticus and with the occurrence of irreversible neurologic deficits. Another important hypothesis is that the occurrence of specific imaging changes, particularly increased T_2 and decreased ADC in the splenium of the corpus callosum, is associated with the development of postictal psychiatric or behavioral changes. This hypothesis could be addressed prospectively by systematically imaging patients who manifest postictal psychosis by using appropriate pulse sequences, and by examining them serially as psychiatric symptoms resolve either spontaneously or with treatment.

Many exciting questions emerge from this review. For example:

- Which imaging findings are cause, which are consequence?
- Are there critical characteristics of seizures or thresholds that determine appearance of periictal changes?
- What is the relation between T_2 and ADC changes?
- What is the significance of distant imaging changes?
- Can we use periictal imaging to detect localizing anatomic changes more reliably?

It is not possible to address these questions effectively by using studies that are typically obtained fortuitously. Rather, it will require a more systematic approach to gathering postictal data prospectively in series of patients with specific epilepsy syndromes. Given the likely insights that

imaging data can provide into pathophysiology and prognosis, it seems worthwhile to invest significant resources in such an undertaking.

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