POSTICTAL PSYCHOSIS: COMMON, DANGEROUS, AND TREATABLE

Orrin Devinsky, MD

Departments of Neurology, Psychiatry, and Neurosurgery, NYU Epilepsy Center, New York, NY

"Occasionally, after a fit, or, more frequently, after a series of fits, an attack of mental disturbance may come on which lasts for several days. It may be simply a demented state, or there may be hallucinations, with irritability and even violence (1)."

Postical psychosis often complicates chronic epilepsy, especially in patients with seizure clusters that include tonic–clonic seizures, bilateral cerebral dysfunction (e.g., bilateral epileptiform activity or history of encephalitis), and a family history of psychiatric illness. Psychosis includes delusions, auditory and visual hallucinations, mood changes, and aggressive behavior. It typically emerges after a lucid interval of hours or days after the last seizure. This treatable disorder is associated with serious morbidity and mortality.

Esquirol, in the first textbook of psychiatry (1838), described postictal "fury," lasting hours to days (2). Hughlings Jackson postulated that postictal "acute attacks of insanity (epileptic mania)" were produced by lower centers that "are healthy except for exaggerated action, consequent on loss or defect of the highest controlling centers, the parts really *diseased* (3)." Interest in epilepsy-related psychoses was rekindled (4,5) by landmark studies on forced normalization by Landolt, published in 1958 (6), and on interictal psychosis by Slater and Beard, published in 1963 (7). After a century of neglect, postictal psychosis (PP) was rediscovered by Logsdail and Toone, in the latter part of the 1980s (8). Antiepileptic drug withdrawal used to induce seizures in epilepsy monitoring units more recently led to increased recognition of PP (9,10). PP comprises approximately 25 to 30 percent of the psychoses of epilepsy (11), even when cases associated with video-EEG monitoring are excluded (12).

Address correspondence to Orrin Devinsky, MD, Departments of Neurology, Psychiatry, and Neurosurgery, NYU Epilepsy Center, 403 E. 34th Street, 4th floor, New York, NY 10016. E-mail: od4@nyu.edu

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Clinical Features

Logsdail and Toone's diagnostic criteria for PP (see Table 1) continue to be widely used (8,10,13). The typical patient is psychiatrically well until a cluster of tonic–clonic seizures, with or without complex partial seizures, occurs (9,10,13,14). After an initial postictal period marked by confusion and lethargy, the patient improves for hours to days (the lucid interval). Subsequently, psychotic symptoms develop and typically last days to weeks (8–10,12,15,16). Although not emphasized in the literature, a degree of confusion and delirium (e.g., impaired attention, alterations in sleep–wake cycle and motor activity, and increased autonomic activity) often coexist with psychotic features. This profile frequently is seen in epilepsy monitoring units, where PP affects between 6 and 10 percent of presurgical candidates (9,16). Further, PP is almost exclusively an adult disorder emerging in the setting of chronic epilepsy. The mean age of onset is 32–35 years (10,12,13,17,18), first occurring at an average of 15–22 years after the onset of epilepsy (12,14,17–19). Most patients have temporal lobe epilepsy (TLE), although case-controlled studies conflict as to whether TLE or partial epilepsy rates are significantly more common.

The lucid interval is a relatively unique feature of PP. Unlike other postictal symptoms, which are maximal immediately after the seizure, as mentioned, PP emerges after seizures cease. There are no detailed studies of the lucid interval, which lasts from 2 hours to a week but usually persisting over 6 hours (8–10). Present in most PP cases, the lucid interval is a diagnostic pitfall. In the monitoring unit, after sufficient seizures are recorded, AEDs are often restarted and patients discharged. Some may have a normal mental state when discharged but develop psychosis at home.

The psychosis is characterized by fluctuating combinations of thought disorder, auditory and visual hallucinations (either may predominate), delusions (grandiose, religious, persecutory), paranoia, affective change (mania or depression), and aggression. Auditory or visual hallucinations can predominate (8,12,13,20,21). Compared to patients with interictal psychosis, those with PP are more likely to suffer visual hallucinations, grandiose and religious delusions, pressured speech, and illusions of familiarity (12). By contrast, referential, perceptual, and persecutory delusions as well as auditory hallucinations of voices are more common patients with interictal psychosis (12). Religious and violent behavior can be prominent in PP (15,22). Most sudden religious conversions in epilepsy patients occur during the postictal period (23). Both verbal and physical violence can occur, which may be serious and life-threatening

TABLE 1. *Logsdail and Toone's Diagnostic Criteria for Postictal Psychosis*

1. Episode of psychosis (often with confusion and delirium), developing within 1 week of a seizure or cluster of seizures;
2. Psychosis lasting at least 15 hours and less than 2 months;
3. Mental state characterized by delirium or delusions (e.g., paranoid, nonparanoid, delusional, misidentifications) or hallucinations (e.g., auditory, visual, somatosensory, olfactory) in clear consciousness;
4. No evidence of:
   a) a history of treatment with antipsychotic medications or psychosis within the past 3 months,
   b) antiepileptic drug toxicity,
   c) an EEG demonstrating nonconvulsive status,
   d) a recent history of head trauma or alcohol/drug intoxication or withdrawal (other than benzodiazepines used for epilepsy).

to the patient or others. In one study of 43 consecutive deaths among patients with well-characterized epilepsy, all six suicides occurred in patients with TLE: three jumped in front of a moving train during PP (24). Other known deaths related to PP include a suicide performed by jumping into the center of a stairwell from the 12th floor of an epilepsy center and a patient stabbing his wife.

Risk Factors for Postictal Psychosis

The literature contains diverse and contradictory risk factors for PP. The most consistent risk factors for PP are evidence of bilateral or widespread CNS injury, including encephalitis, head injury, bilateral interictal epileptiform activity (10,13), borderline intelligence (18), and EEG slowing (13). Seizure clusters that include tonic–clonic seizures are significantly more likely to cause PP than those with only complex partial seizures (10,13,14). Partial epilepsy, especially TLE, is considered a critical risk factor for PP (8,16–18,21). Among case-controlled studies comparing the rate of PP in TLE versus other epilepsy groups, one found a significantly higher rate in TLE patients (18), one found an equal percentage among TLE and idiopathic generalized epilepsy (10), and one found PP more commonly in the extratemporal/nonlocalized group of partial epilepsy patients (13). The laterality of seizure focus, age of onset, and duration of epilepsy have not emerged as significant risk factors (10,13,16,18,25). A family history of mood disorders (13), psychosis (18), specific psychiatric disorders (13), and epilepsy (13) were risk factors for PP. Febrile seizures have been found more (16), less (26), or with equal (13) frequency in patients with PP compared with other epilepsy groups.

Among studies on TLE patients, divergent pathologic entities are associated with PP (16,19). In one study, PP was more common among those with than without unilateral hippocampal sclerosis (16). This study found that significantly more patients with hippocampal sclerosis and PP also had ipsilateral temporal neocortical atrophy. Another study reported that TLE patients with PP had relatively preserved anterior hippocampi and more frequent temporal dysplasia than those without PP (19).

Course and Treatment

Prompt recognition of PP is critical to minimizing morbidity. Many patients with delusions and hallucinations do not spontaneously report symptoms and, thus, may only be identified with specific questions. After seizure clusters, especially those that include convulsions, inquiring about unusual thoughts and behavior can help identify PP. In some cases, seizures occur during sleep or are associated with amnesia (diurnal seizures) and the postictal nature of the psychosis is not readily apparent.

The duration of PP varies from 12 hours to more than 3 months (mean, 9–10 days) (27). Impaired intellectual function and family history of psychosis predict a longer psychosis (17). Although not common, forced normalization, with suppression of interictal epileptiform activity during PP, was associated with prolonged PP ($\geq$12 weeks) in two patients (27). Recurrent PP is seen in 12 percent (25) to 50 percent (14,17) of patients and occasionally may progress to an interictal psychosis (28).

A combination of a benzodiazepine and an atypical antipsychotic drug is often used to treat PP. Early treatment can lead to the rapid resolution of PP. Patients with recurrent PP may be successfully managed as outpatients with this regimen. In cases of multiple recurrences at shorter intervals, ongoing antipsychotic treatment that is increased after seizures may be beneficial. Successful epilepsy surgery can lead to the resolution of PP. However, PP patients may be at higher risk for mood disorders after surgery, especially after dominant temporal lobectomies (29).

Periictal Versus Postictal Psychosis

As detailed in Table 1, Logsdail and Toone's criteria ushered in the modern study of PP but artificially limited the biological spectrum. In addition to classic cases, other psychoses develop periictally. For example, psychiatric changes can precede the onset of seizures and additional seizures can occur during psychosis (30). Such cases may be missed or excluded from many studies, which emphasize cases captured in the artificial setting of video-EEG monitoring. A history of psychiatric symptoms preceding the seizure or seizure cluster should be carefully sought. Spratling's case of periictal religiosity illustrates this phenomenon (31):

> "A man of forty-three years, under my care, whose epilepsy had followed scarlatinal nephritis at the age of seven years, and who was subject to long remissions in his disease, had serial

attacks from three to four weeks apart. The first indication noted of his approaching fits was his fault-finding at the table. He suddenly objected to his neighbor, calling him a vile name. At the next meal he refused to sit beside him and at the next meal failed to appear at all. He was found in his room shortly after, moody, sullen, and irritable, reading the Bible. He kept this up all night and the better part of the following day, when he suddenly lay his Bible aside and began to loudly revile everyone within hearing, in the most profane and violent language. On his finally attempting to assault his nurse and physician, he was placed in restraint. A few hours later, he had three severe attacks in rapid succession, six hours after which he was composed and agreeable to all about him. His malady followed this course for many years."

Pathophysiology

PP is associated with relatively broadly and bilaterally distributed epileptogenic networks as well as genetic determinants of seizures and psychiatric disorders. Predisposing etiologies include encephalitis and head trauma, which often cause bilateral pathology. Bilateral or widespread pathology also is suggested by findings of lower intelligence, bilateral interictal epileptiform activity, and slowing on EEG, as risk factors for PP. The role of bilateral pathology is corroborated by a consecutive series of 282 temporal lobectomies. PP occurred in all three patients with seizure recurrence in the contralateral temporal lobe, while no patients with seizure recurrence in the ipsilateral temporal lobe developed psychiatric disorders (32).

Convulsions, that is, intense seizures affecting both hemispheres, most often precede PP. The approximately 20-year average interval between seizure onset and first psychosis suggests that the cumulative effect of recurrent seizures contributes to the development of PP and helps explain why PP is very rare in children. Supporting the role of chronic and severe epilepsy, two patients with generalized epilepsy who developed PP each had more than 75 lifetime convulsions (10).

Metabolic studies during PP reveal hypermetabolism involving both temporal and frontal lobes (33), the ipsilateral frontal and temporal lobes (25), or lateral temporal areas (34). The consistent findings of increased metabolic activity suggest that PP results from excessive activation, likely as a "rebound" after the initial period of postictal depression. Rebound after withdrawal from CNS depressants may provide a model for PP: the greater the rate and level of CNS depression, the greater the rebound excitation. With epilepsy patients, benzodiazepine withdrawal can produce delirium and psychosis (35). Sustained cortical hyperactivity in the patients with bilateral cerebral dysfunction and genetic predisposition to psychiatric illness may produce psychosis. Excessive excitation in the setting of impaired regulation of emotional and cognitive signals may be critical in the pathogenesis of PP.

Conclusion

PP is a common psychiatric complication of chronic epilepsy. Recognition of this disorder is critical to initiate treatment and avoid significant morbidity and mortality. Seizure control can prevent PP, which is often recurrent and can be associated with progressive interictal behavioral changes. Understanding the pathophysiology of PP could provide unique insights into the mechanisms underlying psychotic disorders.

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