

Peri-Ictal and Para-Ictal Psychiatric Phenomena: A Relatively Common Yet Unrecognized Disorder



Antonio Lucio Teixeira

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Abstract Patients with epilepsy can experience different neuropsychiatric symptoms related (peri-ictal) or not (interictal) with seizures. Peri-ictal symptoms can precede (pre-ictal) or follow (post-ictal) the seizure, or even be the expression of the seizure activity (ictal). Neuropsychiatric symptoms, such as irritability and apathy, are among the most frequent pre-ictal manifestations. Ictal fear is reported by around 10% of patients with focal seizures, and sometimes can be difficult to differentiate from panic attacks. Post-ictal anxiety, mood and psychotic symptoms are also frequently reported by patients. Peri-ictal phenomena can occur as isolated symptom or as a cluster of symptoms, sometimes resembling a full-blown psychiatric syndrome. Actually, peri-ictal and interictal neuropsychiatric manifestations seem to be closely associated.

Keywords Anti-depressants · Anti-psychotics · Apathy · Dysphoric symptoms · Forced normalization · Ictal fear · Ictal symptoms · Interictal symptoms · Irritability ·

A. L. Teixeira (✉)

Instituto de Ensino e Pesquisa, Santa Casa BH, Belo Horizonte, Brazil

Neuropsychiatry Program, McGovern Medical School, Department of Psychiatry and Behavioral Sciences, UTHealth Houston, Houston, TX, USA

e-mail: Antonio.L.Teixeira@uth.tmc.edu

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Para-ictal symptoms · Peri-ictal symptoms · Post-ictal anxiety · Post-ictal depression · Post-ictal psychoses · Post-ictal symptoms · Pre-ictal symptoms

1 Introduction

Patients with epilepsy (PWE) can experience a broad range of behavioral and psychiatric symptoms that are typically categorized according to their temporal relation with the ictus (Ettinger and Kanner 2007; Kanner and Schachter 2008; Kanner 2011; Krishnamoorthy et al. 2007). The symptoms are called **interictal** if there is no temporal association between them and seizure occurrence. **Peri-ictal** symptoms are time-locked to seizures, i.e. they can precede (pre-ictal) or follow (post-ictal) the seizure, or even be the expression of the seizure activity (ictal). Finally, **para-ictal** phenomena refers to psychiatric symptoms that occur in patients with difficult to treat epilepsy following seizure remission or control, being also called “phenomenon of forced normalization” or “alternative psychopathology.”

Peri-ictal psychiatric manifestations have been historically well described in the literature, but they remain much less studied than interictal ones. Nonetheless, they contribute to disability and distress among PWE (Mula and Monaco 2011). Moreover, peri-ictal phenomena can occur as isolated symptoms or as a cluster of symptoms, sometimes resembling a full-blown psychiatric episode. These symptoms may account for noticeable clinical differences in psychiatric presentation between patients with and without epilepsy.

This chapter will review peri-ictal and para-ictal psychiatric phenomena in PWE, also discussing their association with interictal psychopathology. The main features and frequency of these behavioral and/or psychiatric manifestations are presented in Table 1.

2 Peri-Ictal Behavioral Manifestations

2.1 Pre-Ictal Symptoms

Among different potential pre-ictal symptoms (e.g., headache, autonomic changes, etc.), behavioral or psychiatric symptoms are the most frequent, notably irritability and mood changes, such as sadness and apathy. Pre-ictal psychiatric symptoms may precede a seizure by minutes to up to 3 days and might represent the expression of epileptic activity. However, they are not related to scalp electroencephalography (EEG) changes (Mula and Monaco 2011).

In their pivotal study, Blanchet and Frommer (1986) systematically investigated the presence of pre-ictal psychiatric symptoms in 27 patients who were asked to rate their mood daily for a period of 56 days. Dysphoric symptoms were present in 22 of

Table 1 Main features and frequency of behavioral and psychiatric manifestations related to epileptic seizures

Period	Relation with ictus	Duration of symptoms	Main behavioral features	Frequency
Pre-ictal	Before	Three days before to one day after ictus	Irritability, dysphoria, depressed mood	13–81.5%
Ictal	At the moment of ictus	Less than 1 min	Fear Depression Psychosis	10–15% 1% ?
Post-ictal	After	Immediately after to 120 h after the ictus	Psychosis Depression Manic/hypomanic Anxiety	11–15% 18% 22% 33%
Para-ictal	With seizure control	?	Depression Anxiety Psychosis PNES	13–15% 11–15% 4–8% 1.8–10%
Interictal	No relation	–	Depression Anxiety Psychoses Personality disorders	24–74% 10–25% 2–9% 1–2%

the 27 patients (81.5%), and they became worse closer to the seizure (Blanchet and Frommer 1986). More recently, Mula et al. (2010) reported a prevalence of 13% of pre-ictal dysphoric symptoms in PWE, highlighting that such symptoms are clinically similar to interictal ones (Mula et al. 2010).

Since pre-ictal psychiatric symptoms are not easily detected by rating scales or self-administered questionnaires, clinicians must directly investigate them as they can inform about seizure occurrence. This might allow preventive and/or therapeutic anti-seizure measures.

2.2 Ictal Symptoms

Ictal psychiatric symptoms represent focal aware seizures that may be followed by consciousness impairment. In most cases, they are brief, lasting less than 1 min, and associated with motor automatisms and/or post-ictal confusion. They can assume different presentations, including ictal fear, ictal depression, and ictal psychosis.

Ictal fear (IF) is the most frequently reported ictal psychiatric symptom, being reported by around 10% of patients with focal seizures. It typically manifests as a sudden fear at the beginning or during an epileptic seizure, without context or any relation to a precedent perception or cognition. IF duration is usually short, varying from 30 to 60s, and can be accompanied of other ictal signs like motor automatisms and impaired awareness (Feichtinger et al. 2001; Kanner 2004; Beyenburg et al. 2005; Rosa et al. 2006). Its intensity may vary from mild anxiety to an out of

Table 2 Clinical differentiation between ictal fear and panic attack

Clinical feature	Ictal fear	Panic attack
Duration	Usually less than 30 s	Usually between 5 and 10 min
Fear sensation	Usually mild to moderate	Usually intense
Associated symptoms	Autonomic symptoms, including excessive salivation and motor automatisms	Autonomic symptoms, but not excessive salivation
Outcome	Focal aware seizure can evolve with impaired awareness and into secondarily generalized tonic-clonic seizures	Patients can develop agoraphobia in the long term

proportion terror distinguishable from the expected apprehension that accompanies the beginning of a seizure. In some cases, IF can resemble the feeling of someone's presence, be associated with an unpleasant revival of past events or accompanied by autonomic symptoms (tachycardia, hyperventilation, diaphoresis) (Rosa et al. 2006; So 2006). It may also coexist with other manifestations of focal aware seizures, such as epigastric aura, *jamais vu*, and depersonalization (Rosa et al. 2006). IF can be the only manifestation of the patient's seizure, which might lead to the misdiagnosis of panic disorder (Gaitatzis et al. 2004; Chiesa et al. 2007; Guimond et al. 2008; Toth et al. 2010) (Table 2). Although IF has been reported in extratemporal epilepsies (e.g., cingulate gyrus), it is more frequent in patients with mesial temporal lobe epilepsy (MTLE), mostly originating in right structures. Since IF is more frequently associated with epileptic discharges from mesial temporal areas, Feichtinger et al. (2001) investigated the post-surgical seizure outcome of 33 patients with refractory MTLE, 12 of whom experienced IF who underwent an anteromesial temporal lobe resection. Eleven out of the 12 who reported IF (91.6%) became seizure free postoperatively. In contrast, only 11 out of other 21 patients without IF (52.3%) had such favorable outcome. Accordingly, the presence of IF could contribute to the localization of epileptogenic zone in mesial temporal structures, also highlighting the relevance of IF as prognosis marker of surgical outcome (Feichtinger et al. 2001).

Ictal depressive symptoms, including anhedonia, guilt, and suicidal ideation, are the second most frequently reported ictal psychiatric manifestations. They occur as a clinical expression of a focal aware seizure in approximately 1% of patients and more commonly in temporal lobe epilepsy. Typically, ictal symptoms of depression are followed by alteration of consciousness as the ictus evolves from a focal aware to a focal impaired awareness seizure (Kanner and Schachter 2008). At times, these brief mood changes represent the only expression of focal aware seizures and, consequently, may be difficult to recognize them as epileptic phenomena.

Ictal psychoses usually represent the manifestation of a nonconvulsive status epilepticus, either in generalized (or absence) or in focal (with or without impaired awareness) status (Kanner 2011). The duration of symptoms, such as aggressive and disorganized behaviors and visual hallucinations, varies from hours to days. Ictal psychosis of temporal lobe origin is characterized by a more profound impairment of consciousness as compared to extratemporal ones (Nadkarni et al. 2007). Ictal

hallucinations are usually visual and less frequently auditory. PWE also retain some insight that such hallucinatory symptoms are unreal. Interestingly, Devinsky et al. (1989) reported a specific ictal hallucination, namely autoscopic or “out of the body” experiences, showing that these phenomena have a localizing (most originating from the temporal lobes) but no lateralization value (Devinsky et al. 1989).

2.3 *Post-Ictal Symptoms*

Post-ictal symptoms may begin either immediately after the seizure (immediate phase) or more characteristically later (delayed phase), i.e. from 12 h to 7 days after a seizure. Cognitive disorders and headache are typical of the immediate post-ictal phase, while post-ictal psychiatric symptoms occur during the delayed phase. Kanner (2004) determined the frequency of post-ictal psychiatric symptoms in a cohort of patients with refractory partial epilepsy, finding 45% of anxiety, 43% of depression, 22% of hypomania, and 7% of psychosis.

Although post-ictal psychoses (PIP) are not the most frequent post-ictal psychiatric syndrome or symptom, they are the best characterized one. This is, at least in part, due to the fact that PIP are frequently referred for psychiatric assessment, accounting for as much as 25% of cases of psychosis in early series (Kanner 2011; Mula and Monaco 2011). More recent studies assessing psychiatric disorders in patients with resistant MTLE and with juvenile myoclonic epilepsy (JME) have reported psychosis in 11–15% and 3–5% of patients, respectively. PIP represented around 30% and 40% of the diagnoses of psychotic disorders in patients with JME and MTLE, respectively (De Oliveira et al. 2010; De Araujo Filho et al. 2008, 2011). Clinical variables associated with PIP include: long epilepsy duration, secondary generalized tonic-clonic seizures, marked affective component (e.g., manic/hypomanic or mixed mood features) in the presentation, and response to low dose of antipsychotic drugs and benzodiazepines (Adachi et al. 2003, 2007; Kanner and Barry 2001; Elliott et al. 2009). Actually, the typical phenomenology of PIP is marked by grandiose, paranoid, and/or religious delusions in the setting of affective changes, mostly mood elevation. Schizophreniform traits, such as perceptual delusions and auditory hallucinations, including commanding/commenting voices, can be present, but are much less frequent (Kanemoto et al. 1996, 1998; Kanner 2011). It has been proposed that PIP would be a predictor of bilateral ictal foci and, therefore, a clinical marker of poor surgery outcome (Kanner and Ostrovskaya 2008). Conversely, the presence of PIP in patients with unilateral MTLE was associated with favorable post-surgical psychiatric and surgical outcomes. In a retrospective cohort with 115 MTLE patients submitted to cortico-amygdalo-hippocampotomy, PIP was present in four patients (3.6%) and all of them became seizure-free and presented complete remission of psychotic symptoms after surgery (De Araujo Filho et al. 2012a, b).

Compared to PIP, post-ictal mood changes are less frequently studied and recognized in clinical practice. Their prevalence in large populations of PWE

remains to be established. In a monitoring unit, Kanner et al. (2004a) investigated the presence of habitual post-ictal symptoms of depression in 100 consecutive patients with poorly controlled focal seizure disorders (79 patients had MTLE and 21 had seizures of extratemporal origin). Forty-three patients (43%) had a mean of 4.8 ± 2.4 post-ictal symptoms of depression (range = 2–9; median = 5) with a pleomorphic presentation. Thirteen patients (13%) reported post-ictal suicidal ideation; eight of them experienced passive and active suicidal thoughts, while five only reported passive suicidal ideation. In addition, 18% of patients had at least five symptoms of depression lasting more than 24 h, but less than 2 weeks – temporal criterion required by the DSM for a major depressive episode diagnosis (Kanner et al. 2004a). There was a significantly greater number of post-ictal symptoms of depression in patients with an interictal history of depression and anxiety disorders, and a significant association between the occurrence of post-ictal symptoms of depression and prior psychiatric hospitalization primarily due to post-ictal suicidal ideation. A comparison of seizure-related variables between patients with post-ictal depressive episode and patients without any post-ictal psychiatric symptom failed to reveal any differences (Kanner et al. 2004a; Kanner and Schachter 2008; Kanner 2011). Post-ictal depressive symptom or episode may occur despite successful treatment of interictal depressive symptoms, and the only prevention strategy seems to be suppression of seizures (Kanner 2011).

In the aforementioned study, manic/hypomanic symptoms occurred in 22% of 100 patients, frequently with psychotic symptoms (Kanner et al. 2004a). Such manic episodes last longer and have a higher frequency of recurrence than PIP, being associated with EEG frontal discharges and dominant hemisphere involvement (Nishida et al. 2006; Kanner and Schachter 2008).

Post-ictal anxiety is a frequent psychiatric manifestation, being reported by 45 out of 100 patients (45%) in a case series (Kanner et al. 2004a). Of them, 15 (33%) experienced a cluster of four symptoms that lasted at least 24 h. A prior history of anxiety disorder was also identified in 15 patients (33%). There was a significant association between a history of anxiety disorder and the occurrence of two post-ictal symptoms of anxiety: constant worrying and panic feelings. In addition, there was a greater number of post-ictal symptoms of anxiety in the presence of a past history of anxiety and depressive disorders (Kanner and Schachter 2008).

3 Para-Ictal (“Alternative”) Behavioral Manifestations

Para-ictal or alternative psychiatric phenomena refer to de-novo psychotic and/or mood disorders in patients with treatment-resistant epilepsy following seizure remission or control. In 1958, Landolt reported series of patients with treatment-resistant epilepsy who developed de-novo psychotic episodes associated with a remission of their seizures and a normalization of their EEG recordings. This phenomenon was referred to as “forced normalization” (FN) of the EEG. Later, Tellenbach introduced the term “alternative psychosis” to denote the reciprocal relationship between

abnormal mental states and seizures, which did not rely on EEG findings, as Landolt's term did. In either case, since these early studies, several patients with alternating psychosis have been documented (Trimble and Schmitz 1998; Mula and Monaco 2011; Calle-López et al. 2019).

Studies have reported the appearance of para-ictal behaviors in association with the prescription of specific anti-seizure medications, such as barbiturates, ethosuximide, vigabatrin, topiramate, levetiracetam, and zonisamide (Schmitz 2006; Mula and Monaco 2009; Chen et al. 2017; Calle-López et al. 2019). Other series described para-ictal phenomena, such as *de-novo* psychotic, depressive and anxiety symptomatology, following epilepsy surgery in patients reaching seizure control (De Araujo Filho et al. 2012a, b; Ramos-Perdiguez et al. 2018; Calle-López et al. 2019). FN has also been associated with para-ictal psychosis secondary to vagus nerve stimulation, suggesting that the mechanisms underlying the control of seizures are inextricably linked to those of psychosis (Gatzonis et al. 2000; Schmitz 2006; Mula and Monaco 2011).

There is no specific or prototypical presentation of this phenomenon. In 44 cases of FN described by Wolf (1991), the commonest psychiatric syndromes were psychosis while dysphoria marked by restlessness and anxiety was also frequent. Studies have also proposed that the symptomatology is often determined by personality structure, psychiatric history, or familial predisposition (Mula and Monaco 2011). In a recent systematic review, the clinical and sociodemographic data of 193 episodes of FN were evaluated (Calle-López et al. 2019). Sixty percent of PWE were female, with a mean age of 28.3 ± 14.2 years. The majority had focal (80%) symptomatic (44%) epilepsy. Most patients reported a high seizure frequency (58%) and were on polypharmacy (51%). Patients presented psychosis (86.4%), mood disorders (25.8%), and dissociative disorders (4.5%) as the main psychiatric manifestation. In the psychosis group, persecutory delusions (52.6%) and referential thinking (47.3%) were the most frequent symptoms. FN was provoked by an anti-seizure medication (48.5%), mainly levetiracetam, epilepsy surgery (31.8%), or vagus nerve stimulation (13.6%). Treatment included anticonvulsant withdrawal (47%) or taper (25%), and antipsychotics were initiated in the majority of cases (73%). Psychiatric symptoms were partially controlled in 35%, with complete resolution of symptoms in the remaining 65% of cases. Most patients (87%) with anti-seizure medication-triggered FN had complete resolution of psychiatric symptoms following their discontinuation in comparison with 28.5% of patients with surgery-triggered FN [36]. Antipsychotic drug use did not result in symptom remission as much as anti-seizure medication discontinuation. Although there was a positive response to treatment in patients with FN triggered by drugs, the prognosis was more reserved in patients with surgery-triggered FN (Calle-López et al. 2019).

4 Association Between Peri-Ictal and Interictal Behavioral Manifestations

Studies have consistently reported high prevalence of interictal psychiatric disorders in PWE, particularly among those with pharmaco-resistant MTLE, with numbers ranging from 20 to 70%. Mood disorders have been observed as the most common interictal psychiatric disorders (24–74%), followed by anxiety (10–25%), psychosis (2–9%), and personality disorders (Gaitatzis et al. 2004; De Oliveira et al. 2010, 2011, 2012; De Araujo Filho et al. 2012a, b; Mula et al. 2008).

Although the association between interictal psychopathology and peri-ictal behavioral manifestations has not been thoroughly investigated, the available evidence suggests that they are closely related. While interictal symptoms constitute a risk factor for the development of peri-ictal psychiatric symptoms, post-ictal psychopathology contributes to the development of chronic psychiatric conditions (Mula and Monaco 2011). One important related issue is the potential peri-ictal exacerbation of interictal symptoms, which seems to happen in most patients.

In this context, studies have identified a discrete condition marked by interictal symptoms of depression and anxiety that worsened in severity during the post-ictal period, referred to as interictal symptoms with a post-ictal exacerbation (ISPE). Interictal depression, anxiety, and neurovegetative symptoms with post-ictal exacerbation were identified in 36 of 100 patients, with 19 of those 36 (52.7%) presenting only ISPE, while the remaining 17 had both ISPE and interictal symptoms (Kanner et al. 2004b; Kanner and Schachter 2008; Kanner 2011). Among 36 patients with ISPE, thirty (83%) experienced distinct post-ictal symptoms of depression or anxiety. In 13 patients, antidepressant medication was started for the treatment of post-ictal symptoms of depression and anxiety but failed to prevent them. An important clinical factor associated with the occurrence of ISPE and post-ictal symptoms of depression and anxiety was poor seizure control, which might account for the patient's perceived chronic dysphoric states. Alongside this persistent dysphoria, post-ictal symptoms negatively affect the patient's perception of his/her quality of life (Kanner et al. 2004b; Kanner and Schachter 2008; Kanner 2011).

Anti-seizure medications with GABAergic properties (e.g., benzodiazepines, barbiturates) may contribute to post-ictal exacerbation of interictal symptoms (Ettinger and Kanner 2007; Kanner and Schachter 2008; Mula and Monaco 2011). From a therapeutic perspective, it is worth mentioning that while antidepressants do not prevent the development of post-ictal mood symptoms, antipsychotics seem to be effective for post-ictal psychosis (Kanner 2011). This failure of post-ictal depressive symptoms to respond to standard pharmacological strategies suggests different underlying pathogenic mechanisms compared to interictal and/or idiopathic psychiatric disorders (Kanner et al. 2004b; Kanner and Schachter 2008).

5 Conclusion

The current chapter reviewed peri-ictal and para-ictal psychiatric and behavioral symptomatology occurring in PWE, illustrating the high frequency of such symptoms and their association with interictal conditions. Recognition of peri-ictal episodes is of paramount importance as they may have a negative impact on the quality of life of patients. Unfortunately, post-ictal psychiatric symptoms are rarely investigated in clinical practice. The recognition of these phenomena represents the essence of the neuropsychiatry of epilepsy. Missing their diagnoses might have practical implications regarding prognosis and therapeutics, issues that must be better investigated in research settings. Finally, the atypical characteristics of peri-ictal and para-ictal psychiatric symptoms or clusters of symptoms require that screening instruments and structured psychiatric interviews be developed specifically for PWE.

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