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Review Article

Epilepsy and Psychosis

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Abstract

Psychosis is a significant comorbidity for a subset of patients with epilepsy, and may appear in various contexts. Psychosis may be chronic or episodic. *Chronic Interictal Psychosis* (CIP) occurs in 2-10% of patients with epilepsy. CIP has been associated most strongly with temporal lobe epilepsy. Episodic psychoses in epilepsy may be classified by their temporal relationship to seizures. *Ictal psychosis* refers to psychosis that occurs as a symptom of seizure activity, and can be seen in some cases of non-convulsive status epilepticus. The nature of the psychotic symptoms generally depends on the localization of the seizure activity. *Postictal Psychosis* (PIP) may occur after a cluster of complex partial or generalized seizures, and typically appears after a lucid interval of up to 72 hours following the immediate postictal state. Interictal psychotic episodes (in which there is no definite temporal relationship with seizures) may be precipitated by the use of certain anticonvulsant drugs, particularly vigabatrin, zonisamide, topiramate, and levetiracetam, and is linked in some cases to "forced normalization" of the EEG or cessation of seizures, a phenomenon known as *alternate psychosis*. Seizures and psychosis may also co-occur secondary to another neurologic disorder, such as a traumatic brain injury, brain tumor, or limbic encephalitis. When a patient with epilepsy develops psychosis, the clinician should attempt to determine the cause, as treatment approach may vary. In this article, we review the various forms of epilepsy-related psychosis and discuss a rational approach to the evaluation and management of patients with epilepsy and psychosis.

ABBREVIATIONS

CIP: Chronic Interictal Psychosis; PIP: Postictal Psychosis; SLPE: Schizophrenia-Like Psychosis of Epilepsy; TLE: Temporal Lobe Epilepsy; ASE: Absence Status Epilepticus; APD: Antipsychotic Drug; EEG: Electroencephalogram

INTRODUCTION

An association between epilepsy and mental illness has been recognized for centuries, but the true nature and causes of that relationship remain poorly understood. In ancient times, like many diseases, epilepsy and mental disorders were attributed to supernatural forces. The Hippocratic authors attempted to counter these beliefs and provide natural explanations as early as 400 B.C., arguing in the book *On the Sacred Disease* that brain is the organ of all psychic processes, normal and pathological, and that not only is epilepsy a disease of the brain, but that all mental diseases are brain diseases as well [1]. Nevertheless, supernatural beliefs persisted. As Late Antiquity gave way to the early middle Ages, epilepsy and insanity both became associated with demonic influences, and this contributed to the stigma associated with both that persisted throughout the Middle Ages and even into the modern era [2,3]. As the influence of astrology spread to Europe from the east, explanations for epilepsy and insanity tended to invoke the effects of the moon. The term "lunacy" came to refer to both conditions, and although its original meaning may have been epilepsy, the term later became associated primarily with mental illness [4].

In the 19th century, patients with epilepsy were housed in asylums together with the mentally ill, which led to an opportunity to study the overlap in symptomatology between the two groups of patients. In the early 19th century, Esquirol (1772-1840), a French psychiatrist, observed a temporal relationship between insanity and seizures. He described an "epileptic mania" that could occur before, after or independently of seizures [5]. The French psychiatrist Benedict Morel published cases in 1860 of paroxysmal behavioral disturbances, most of which involved criminal activities that he considered to be "epileptic equivalents." He characterized these behaviors as a masked or larval form of epilepsy called *épilepsie larvée* that could exist without typical epileptic seizures and be diagnosed by the "main symptoms of epileptic insanity" [5]. However, the existence of *épilepsie larvée* as an entity was subsequently called into question, and is no longer considered a valid construct [6]. In the 1860s, it was theorized that "fright" and "moral" factors were major etiologies for epilepsy [1], which was, in some sense, still viewed as a behavioral disorder. Thus, when considering the historical association between psychosis and epilepsy, it is necessary to attempt to distinguish empirical and evidence-based analyses from the misconceptions and unscientific theories that have historically interfered with our understanding of these illnesses.

DEFINITIONS AND NOSOLOGY

The term psychosis generally refers to a disturbance of specific cognitive functions leading to a distorted perception of reality, and characterized by delusions, hallucinations or both. Delusions are fixed false beliefs that are not amenable to change in response to contrary evidence. Hallucinations are perceptual experiences that occur without an external stimulus. The term psychosis is sometimes used more broadly to include disorganized thinking and catatonic behavior, common symptoms of schizophrenia-spectrum disorders. Strictly speaking, hallucinations are not considered to be manifestations of psychosis when the patient is able to recognize them as such, as is typical of certain types of epileptic perceptual experiences, but the distinction between psychotic and non-psychotic hallucinations is not always clear, and patients with psychotic disorders who initially respond to their hallucinations as if they are real may come to recognize their hallucinatory nature when treated. The spectrum of epileptic hallucinations will be considered in this article.

The epilepsy-related psychoses may be either chronic or transient and occurs in various clinical contexts (Table 1). Transient psychoses that bear a temporal relationship to seizures can be considered ictal or postictal, although the distinction is not always clear. In these cases, the seizures and the psychosis are generally believed to be causally related. Psychosis that bears no temporal relationship to seizures is termed interictal. Interictal psychoses of epilepsy include anticonvulsant-associated psychosis, psychosis following epilepsy surgery, and a chronic interictal form of psychosis that resembles schizophrenia and may be indistinguishable from it. Additionally, epilepsy and psychosis may co-exist as a result of another neurologic condition such as limbic encephalitis or traumatic brain injury.

CHRONIC INTERICTAL PSYCHOSIS OF EPILEPSY

Chronic Interictal Psychosis (CIP) occurs in 2-10% of patients with epilepsy, a rate that is greater than would be expected by chance alone [7]. There is a 2 to 2.5-fold increased risk of schizophrenia and schizophrenia-like psychosis in patients with epilepsy [8,9]. A history of febrile seizures progressing to epilepsy has been associated with a 3-fold increased risk of developing schizophrenia [10]. An association has been drawn between psychosis and Temporal Lobe Epilepsy (TLE) [11], and in particular, left TLE, but this remains uncertain and controversial, and psychosis has been reported in association with generalized epilepsy as well as other focal epilepsies, most notably frontal lobe epilepsy [12]. CIP typically follows the onset of epilepsy by a decade or more [11,13,14], contributing to the notion that the epilepsy may be related to the development of psychosis. Of course, an equally plausible explanation for the association is that in some of these patients, the psychotic illness and the epilepsy share a causal relationship with a third factor such as birth trauma, head injury, or some other developmental or genetic abnormality [15]. Epileptic seizures are manifestations of an underlying aberration of neural circuitry that may result from a wide variety of cerebral pathologies, some of which can be extremely subtle and difficult to identify without pathological tissue. It therefore stands to reason that the underlying cerebral pathology could contribute to the development of psychosis regardless of whether or not seizures are a prominent feature of the patient's history. Nevertheless, it is possible that the types of pathologies likely to produce epileptic seizures (i.e. abnormalities in the structure of the neocortex and limbic system, and particularly those involving the temporal lobes) may also have the potential to lead to the development of a psychotic illness.

Table 1: Psychoses of Epilepsy.

- Chronic Interictal Psychosis
- Episodic/Transient Psychoses of Epilepsy
  - Episodic Interictal Psychosis
  - Psychosis related to seizure
    - Ictal psychosis
    - Postictal psychosis
  - Psychosis related to epilepsy treatment
    - Anticonvulsant-associated psychosis
    - Forced Normalization/Alternate Psychosis
    - Psychosis following epilepsy surgery
- Psychosis and epilepsy secondary to another neurologic disease
  - Cerebrovascular disease
  - Trauma
  - Neoplasm
  - Inflammatory/infectious diseases
  - Metabolic/Genetic diseases
  - Neurodegenerative diseases
  - Effects of exogenous toxins

Slater and Beard in their early descriptions of chronic interictal psychosis of epilepsy emphasized both its similarity to schizophrenia and its existence as an entity distinct from schizophrenia, by referring to it as Schizophrenia-Like Psychosis of Epilepsy (SLPE) [14,16]. Psychosis appears to develop slightly later in persons with epilepsy (mean age 30.1) than in schizophrenia (mean age 26.6) although when only patients with chronic interictal psychosis are considered, the age of onset is similar to that of schizophrenia, while postictal psychosis and episodic interictal psychosis tends to begin at a later age [17]. Patients with SLPE may lack the pre-morbid personality abnormalities seen in patients with schizophrenia [16], may exhibit a greater degree of affective symptomatology than is typical in schizophrenia [18], may be less likely to demonstrate negative symptoms, and may be more responsive to lower doses of neuroleptics [19]. On the other hand, neuropsychological profiles are similar between patients with SLPE and schizophrenia [20], and in many patients, the psychotic syndrome may meet criteria for schizophrenia, even including Schneider's first-rank symptoms [18]. Thus, while there may be some differences in psychopathology between patients with schizophrenia and those with SLPE, the distinctions are subtle and may not be apparent in an individual patient. Some of the difficulty in determining whether SLPE is, in fact, distinct from schizophrenia, can be attributed to changing concepts of schizophrenia over the past several decades. Schizophrenia is increasingly recognized as a heterogeneous disorder that lies on a spectrum with other psychotic illnesses [21]. Functional and structural neuroimaging studies have tended to show predominantly left temporal dysfunction and volume loss, although this has been an inconsistent finding [22].

EPISODIC PSYCHOSES OF EPILEPSY

Transient or episodic psychoses occur in association with

epilepsy. These psychotic episodes more closely resemble "brief psychotic disorder" [23] than schizophrenia due to their limited duration. Conceptually, these psychotic episodes can be categorized according to their temporal relationship to the ictus. Ictal psychosis is a direct manifestation of ongoing seizure activity, while postictal psychosis is a brief psychotic episode that occurs within a week following a seizure or a cluster of seizures. An episodic form of interictal psychosis has also been described and should probably be distinguished from SLPE due to the better prognosis [11], although many studies examining interictal psychosis in general have not specified the duration of the psychosis in their inclusion criteria and may have included these patients with the SLPE patients in their analyses. Among the episodic interictal psychoses are AED-induced psychosis, and forced normalization/alternate psychosis. These will be discussed below.

Ictal hallucinations

Hallucinations are common manifestations of some types of focal seizures [24], although they rarely reflect a truly psychotic state, since the patient usually is able to distinguish the spurious percept from the external world. These hallucinations tend to be brief and may not lead the patient to seek medical attention until more disturbing ictal symptoms have occurred such as alterations of awareness or convulsions. Ictal hallucinations are often recognized as immediate precursors to clearly-identified seizures and are thus referred to as epileptic auras.

Focal parietal lobe seizures may manifest as paresthesias or a sensation of heat or running water that may spread rapidly from one body part to another. Rarely, a patient will report pain or a burning sensation. Insular seizures can produce abdominal sensations. Seizures involving the transverse temporal gyri (Heschl's convolutions) may produce simple auditory hallucinations such as hissing, roaring or buzzing sounds, and seizures involving the superior temporal convolution or other auditory association areas may produce more complex auditory hallucinations such as voices or melodies [25,26]. Seizures in the occipital lobe can produce brief hallucinations characterized by flickering lights, flashing colors (usually red, yellow green or blue), or a brightly colored ball of light [27]. When seizures involve the visual association cortices, they may be more colorful and complex, but insight is usually preserved. Palinopsia may occur, in which images persist or reduplicate. Occasionally, when the seizure involves the occipitotemporal region, images will appear to change size or shape, and the patient may perceive himself as if outside his own body (autoscopy). Complex auditory and visual hallucinations typically do not occur unless there is involvement of limbic structures (e.g. hippocampus and/or amygdala and related cortices), and there is often an affective component to the experience [24]. Olfactory and gustatory hallucinations are also primarily associated with seizures emanating from or involving the limbic structures in the mesial temporal lobe. Limbic seizures may also manifest with primarily emotional symptoms such as anger or fear in the absence of a percept. Wieser described a rage attack and a laughing fit each associated with prolonged runs of epileptic discharges in the left periamygdalar region [28].

Psychotic symptoms in non-convulsive status epilepticus

Patients with *absence status epilepticus* (ASE) typically exhibit an altered state of consciousness with cognitive slowing, verbal and motor impersistence or perseveration, but with preserved ability to respond to simple commands, withdraw from pain, eat, drink and walk. The patient may exhibit clumsiness, automatic behavior, perplexity, and decreased spontaneity with either mutism or poverty or slowness of speech. Amnesia for the episodes is variable. ASE may be provoked by administering drugs such as carbamazepine [29,30], or tiagabine [31] that are known to provoke absence seizures in patients with generalized epilepsy syndromes. It can also occasionally be seen 'de novo' in the setting of benzodiazepine withdrawal [32]. During focal status epilepticus of the frontal pole, the patient may exhibit confabulation and hilarity, while during temporal lobe status epilepticus, the patient is more likely to show symptoms of fear, anxiety, irritabilitity, or aggression [33]. Trimble [34] reported a case of a 22 year old man with a history of complex partial and generalized tonic-clonic seizures since the age of 3 who presented with the sudden onset of a belief that rays were being passed through his body to sterilize him along with auditory hallucinations of voices criticising him. An EEG with sphenoidal electrodes showed rhythmic sharp waves phase-reversing in the right sphenoidal leads. There was rapid resolution of both the psychotic symptoms and EEG abnormalities with intravenous diazepam leading to a diagnosis of ictal psychosis secondary to focal non-convulsive status epilepticus.

Postictal Psychosis

Postictal Psychosis (PIP) has been a recognized phenomenon since the 19th century when Esquirol described postictal "fury" in 1889. Various case series have been reported since then. In 1988, Logsdail and Toone proposed a set of diagnostic criteria along with series of 14 patients with PIP [35]. Their criteria required that the episode occurred immediately following a seizure or within a week of the return of apparently normal mental function and lasted between 24 hours and 3 months. They excluded patients with a history of interictal psychosis, EEG evidence of status epilepticus, evidence of anticonvulsant toxicity, or recent head injury or intoxication, but they included patients with primarily clouding of consciousness, disorientation or delirium in addition to those with delusions or hallucinations in clear consciousness. Subsequent authors have borrowed or adapted these criteria, but some authors have tended to include only patients with delusions or hallucinations in the presence of relatively clear consciousness. A lucid interval following the seizure(s) may be necessary to clearly delineate the syndrome from a postictal confusional state [36].

PIP is most commonly seen in patients with longstanding pharmacoresistant epilepsy and typically occurs after a cluster of convulsive or complex partial seizures. After resolution of the immediate postictal state, there is typically a lucid interval of up to 72 hours [37] followed by onset of psychosis, which typically lasts less than one week and rarely longer than two. The psychosis tends to be affect-laden, with frequent hypomanic or manic features. Paranoia and grandiose or religious delusions are also common [38].

EEG should be strongly considered to evaluate for non-convulsive seizures, but scalp electrodes may be inadequate to fully exclude ictal psychosis, as ongoing focal limbic seizures may not be detectable at the scalp. This has led some to theorize that at least some cases of apparent postictal psychosis may actually be ictal [33,39,40], although this is unlikely to be true for all cases [41]. The difficulty in determining whether a psychotic episode should be considered ictal without intracranial EEG has led some to use the terms "episodic psychosis of epilepsy" or "peri-ictal psychosis" in order to avoid classifying the episode as ictal or postictal [5]. This conservative approach is one way to avoid misclassification, but it likely obscures the distinction between pathophysiologically different entities that may warrant different treatments. It has also been proposed that PIP be separated into a "nuclear" type that is not due to ongoing subclinical seizure activity and is clinically characterized by a lucid interval following the last seizure, and a "peri-ictal" psychosis in which no lucid interval is present and ongoing or recurrent intermittent seizure activity should be suspected [33,36,40]. A volumetric neuroimaging study in PIP showed thickening of the rostral anterior cingulate cortex and middle temporal gyrus [42]. PIP is more likely to occur in patients with bilateral independent ictal foci [43,44], which may suggest that patients who have widely distributed network dysfunction are more prone to the condition.

PIP is self-limited as long as seizures are controlled, so supportive treatment may be all that is necessary, but if the psychosis is severe enough to require pharmacological treatment; it typically responds to benzodiazepines or low-dose atypical antipsychotic drugs [38]. PIP is theoretically preventable, if seizures can be controlled. However, it is often recurrent, and some patients with recurrent PIP may go on to develop CIP [45]. PIP needs to be distinguished from alternate psychosis and psychosis secondary to anticonvulsant drugs.

PSYCHOSIS ASSOCIATED WITH EPILEPSY TREATMENT

Forced Normalization and Alternate Psychosis

The concept of forced normalization was first proposed by Landolt in 1953 to describe an observation that some patients develop psychosis as the EEG normalizes [46,47]. Landolt reported on a series of 107 patients with epilepsy and psychosis, 47 of whom demonstrated this phenomenon. Alternate psychosis describes a related clinical observation that does not depend on EEG data in which psychosis emerges when seizures abate. It has been theorized as a result of these observations that some degree of epileptiform activity may be protective against psychosis in some individuals. This has led some to treat the psychosis by reducing or withdrawing anticonvulsant therapy. The existence of this phenomenon remains controversial. Since in some cases of ictal psychosis, seizure activity is detectable only with depth electrodes and may be associated with generalized attenuation or disappearance of interictal spikes on scalp EEG, it has been proposed that forced normalization may actually reflect ongoing seizure activity restricted to a deep focus [5,33,48].

Psychosis associated with anticonvulsant drugs

Forced normalization/alternate psychosis may also be difficult to distinguish from anticonvulsant-associated psychosis. Drug-induced psychosis should be suspected if the psychosis occurs after addition of a new drug and resolves when the patient is transitioned to an alternative drug despite remaining seizure-free. Certain drugs are more likely those others to induce psychosis. Psychosis has been most closely associated with vigabatrin, but has also been known to occur with zonisamide, ethosuximide, tiagabine, topiramate, and levetiracetam. Rates of psychosis associated with vigabatrin range from 2-5% [47,49]. In a meta-analysis of controlled vigabatrin trials, 2.5% developed psychosis compared to 0.3% of the placebo group [50]. Thomas and colleagues examined 81 cases of behavioral disturbance associated with vigabatrin and found that 28 met criteria for psychosis. Psychosis was associated with a more severe epilepsy, a right sided EEG focus, and suppression of seizures [51]. Psychosis in the setting of ethosuximide use has also been associated with forced normalization/alternate psychosis, and a number of the cases described by Landolt were associated with ethosuximide administration.

Reported rates of psychosis related to topiramate exposure have varied from 0.8% to 12% [47,52], and appear to depend on the dose and the rapidity with which the dose is escalated as well as the presence of a family psychiatric history [53]. Rates may be significantly higher than those seen with lamotrigine and gabapentin [52], and seem to be related to the other cognitive side effects of topiramate. Zonisamide, a drug with a similar side effect profile to topiramate, has been associated with a rate of psychosis of about 2% in two Japanese studies [54]. Miyamoto et al. [55] reported on 74 patients taking zonisamide, among whom 14 (19%) developed psychotic episodes, considerably higher than the expected rates. They found that psychosis was most common in younger patients. In many of the patients, the psychosis did not develop until many months or years had elapsed. Thus, it was difficult to attribute the psychosis to zonisamide, but it was believed that zonisamide increased the risk for psychosis. In a case-control study, Noguchi et al. [56] examined risk factors for development of a first psychotic episode after the addition of a new anticonvulsant drug. They found that among 38 patients with psychosis and 212 control patients, use of zonisamide and phenytoin was significantly associated with psychosis, as were low intelligence and complex partial seizures.

Levetiracetam has been associated with a rate of psychosis of 0.7-1.4% depending on the duration of follow-up and whether or not patients with prior psychiatric history are included [57]. Mula et al. [58] examined psychiatric adverse events prospectively among the first consecutive patients to take levetiracetam at the tertiary referral epilepsy clinics at the National Hospital for Neurology and Neurosurgery in the United Kingdom. Among 517 patients, 6 patients (1.2%) developed psychosis. It is believed that patients with previous psychiatric illness are particularly susceptible to psychiatric side effects of anticonvulsants, and the nature of the previous illness is highly associated with the type of adverse psychiatric drug effects [59]. Since patients with significant psychiatric history are often excluded from initial anticonvulsant trials and were excluded in the analysis of Mula et al., the rates seen in these studies may underestimate the rates seen in current clinical practice. Nevertheless, a retrospective database review of 553 patients with epilepsy receiving levetiracetam identified only 3 patients (0.5%) who discontinued

the drug because of psychosis or hallucinations. This study examined reasons for drug discontinuation and may not reflect psychotic episodes that did not precipitate discontinuation of the drug (for example if the episodes were not attributed to levetiracetam).

Psychosis following epilepsy surgery

Patients with CIP are unlikely to improve significantly following epilepsy surgery, although PIP can theoretically be prevented with successful epilepsy surgery. There is an approximately 7% incidence of de novo psychosis following temporal lobectomy for epilepsy that tends to occur within the first year following surgery [60]. Post-surgical psychosis may be more likely to occur in those with early onset epilepsy and abnormal pre-morbid personality traits [61]. Some studies have suggested a preponderance of right-sided temporal lobe surgeries among patients with post-surgical psychosis, but this has not been supported by later studies [60].

When episodic psychoses occur in patients with epilepsy, an effort should be made to differentiate PIP from treatment-associated psychoses such as alternate psychosis or drug-associated psychosis. The treatment implications are quite different for PIP where suppression of seizures is paramount and withdrawal of an anticonvulsant could conceivably worsen the problem. PIP is more likely if the psychosis occurs after a cluster of seizures when a drug is withdrawn [62]. However, in some cases it can be difficult to distinguish PIP from a drug effect or from alternate psychosis if a new drug has just been started resulting in cessation of seizures. Drug-induced psychosis should be considered whenever psychosis emerges immediately after the addition of a drug to which the patient is naive. Alternate psychosis or PIP should be considered if psychosis recurs with different anticonvulsants or non-pharmacological therapies. Ultimately, though, many of these episodic psychoses may be multifactorial and difficult to place in a particular category. Certain drugs may predispose patients to develop alternate psychosis/forced normalization or PIP more than other drugs. Similarly, patients with a past history of psychosis are more likely to develop psychosis with new drugs [59]. Thus, specific situational factors such as a limbic seizures or specific drugs may contribute to the development of a psychotic state, either in isolation or in combination, in certain patients who are susceptible because of pre-existing structural or genetic factors.

EPILEPSY AND PSYCHOSIS SECONDARY TO AN ACQUIRED NEUROLOGICAL CONDITION

When psychosis and epilepsy occur together in the same patient, a neurologic cause common to both must be sought, particularly when the psychosis precedes the onset of epilepsy. Pathology of the temporal lobes has a tendency to cause both epilepsy and psychosis [63]. Traumatic brain injury may significantly increase the risk for both psychosis and epilepsy, particularly when the temporal lobes are affected. Similarly, tumors involving the temporal lobes may cause both seizures and psychosis. Stimulant drugs such as cocaine or amphetamines may trigger both psychosis and seizures, particularly in susceptible individuals [64-67]. Withdrawal from benzodiazepines and alcohol can also trigger seizures as well as psychosis. Strokes and neurodegenerative diseases such as Alzheimer's disease are common neurological disorders that may increase the risk both for seizures and for psychosis. Much less commonly, limbic encephalitis may cause both conditions, often with a dramatic acute or subacute onset [68] and can occasionally be misdiagnosed as an idiopathic psychotic disorder during its early stages [69]. This is particularly the case with limbic encephalitis secondary to anti-NMDAR antibodies, which tends to occur in young women in association with occult ovarian teratomas, and in which psychosis is a prominent early symptom [70].

When to suspect epilepsy in the setting of new onset psychosis

The above discussions have focused primarily on the various contexts in which psychosis may occur in the setting of a previously diagnosed seizure disorder. However, from time to time, an undiagnosed seizure disorder may be suspected in a patient with new onset psychosis, particularly when the nature of the psychotic presentation is atypical for a primary psychiatric disorder. When new psychiatric symptoms appear, the psychiatrist is tasked with evaluating and excluding a psychosis secondary to a medical condition before a primary psychiatric disorder can be diagnosed [23]. A careful history must be obtained to assess for convulsive seizures or recurrent discrete episodes of alteration of awareness or loss of consciousness, particularly when there is a clear onset and offset and a return to normal mental status in between. Collateral history is often necessary, as psychotic patients may be unreliable historians. Seizures may occasionally be misdiagnosed as thought blocking, catatonia, or responding to internal stimuli, if a clinician assumes a primary psychotic disorder and does not consider alternative possibilities. Seizures should be considered if a patient has a known neurological disorder associated with epilepsy, and if the psychotic symptoms are associated with prominent confusion or other neurological signs. Seizures may also be considered in the differential for recurrent brief psychotic episodes with return to baseline in between [71]. Focal temporal lobe pathology may be suspected by the presence of significant anterograde amnesia, aphasia or a visual field upper outer quadrantanopsia ("pie in the sky"). As the above discussions should make clear, psychotic symptoms can rarely be considered truly secondary to epilepsy, except perhaps, in some cases of ictal or postictal psychosis. More commonly, the presence of seizures indicates the existence of some underlying neuropathology that may be contributing to the behavioral symptomatology. Routine screening of patients with new onset psychosis with EEG is low-yield [72] and should be reserved for patients at high risk.

Approach to the epilepsy patient with new onset psychosis

When a person with epilepsy develops a new onset psychosis, the evaluation and management typically requires collaboration between a neurologist and a psychiatrist. An effort should be made to ascertain whether the psychosis falls into one or multiple of the above-described categories. A careful history should be obtained to determine whether the psychosis followed a seizure or a change in anticonvulsant drugs. A prior history of psychotic episodes should be sought, as should any personal

or family history of psychiatric illness or substance abuse. An EEG, or possibly continuous EEG monitoring, should be obtained to evaluate for non-convulsive seizures or normalization of interictal discharges. A basic laboratory evaluation for new onset psychosis should be conducted, including a complete blood count, serum electrolytes, liver, kidney and thyroid function tests, and a urine toxicology screen for drugs of abuse [63]. Anticonvulsant levels should be measured to evaluate for drug toxicity. If the patient has not had recent brain imaging, or if the epilepsy is secondary to a potentially progressive neurologic disease, a brain MRI scan should be considered. Drugs that have recently been started should be considered potential precipitants for the psychosis, and the patient's anticonvulsant regimen should be reviewed and adjusted, if possible, to remove any agents associated with an increased risk of psychosis. Among the anticonvulsant drugs, the agents that appear to have the most favorable psychiatric profile include valproic acid, lamotrigine, carbamazepine, oxcarbazepine, gabapentin and pregabalin [47]. If treatment with an antipsychotic drug (APD) is necessary, drug-drug interactions with the patient's anticonvulsants should be considered. Enzyme-inducing anticonvulsants (i.e. phenytoin, carbamazepine, Phenobarbital, primidone) may decrease the levels of several APDs such as clozapine, haloperidol, olanzapine, quetiapine, risperidone, and ziprazidone, potentially necessitating higher doses to achieve therapeutic effect [73]. Clozapine should be avoided as it has a greater propensity than other APDs to induce seizures [74].

CONCLUSION

Epilepsy and psychosis co-exist in various clinical contexts. Psychosis may occur in association with seizure activity or it may occur in association with epilepsy treatments. In other cases, seizures and psychosis may occur as symptoms of an acquired, genetic or neurodevelopmental disorder that may or may not be identifiable. The relationship between epilepsy and psychosis is complex, and in many cases, the cause of the psychosis is multifactorial. Psychosis is most likely to occur in the setting of seizures or other types of pathology involving the temporal or frontal lobes, and with exposure to certain drugs, particularly, when there is genetic or neurodevelopment susceptibility. Future research is needed to clarify the role played by genetic predisposition and seizure localization and lateralization in the genesis of epilepsy-related psychosis. Given the significant morbidity associated with psychosis and its potential impact on epilepsy management, it is worthwhile for neurologists and psychiatrists who provide care to patients with epilepsy to be familiar with the various settings in which psychosis may manifest in these patients, and to have a framework in mind for how to approach this problem.

CONFLICT OF INTEREST

Dr. Weisholtz reports no financial disclosures. Dr. Dworetzky consults for Best Doctors and for Sleep Health.

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