The relationship between epilepsy and psychoses has long been debated, and descriptions regarding symptoms of interictal psychoses in patients with epilepsy date back to even the Babylonian era. However, scant attention has been paid to this issue lately. Adequate recognition of psychoses in epilepsy is essential for physicians caring for the affected patients, because the impact on their quality of life is too devastating to be overlooked.

In this review, current knowledge regarding schizophrenia-like psychoses of epilepsy is examined in light of the questions posed by Slater and colleagues.

Key words: epilepsy, interictal psychoses, schizophrenia

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1. Introduction

The relationship between epilepsy and psychoses has long been debated, and descriptions regarding symptoms of interictal, or so-called “schizophrenia-like”, psychoses of epilepsy date back to even the Babylonian era. Even when many diseases were already known to have a natural cause, seizures remained ascribed to supernatural invasion of the body by demons [1]. The ancient Greeks later attributed epilepsy to divine intervention and called it “the Sacred Disease”. However, Hippocrates pronounced otherwise, suggesting that epilepsy was a disorder of the brain, as was madness [2], although it was not until the nineteenth century that our notion of epilepsy was first defined scientifically by Hughlings Jackson [3].

Investigations of associations between epilepsy and psychoses were initially conducted by French alienists and later followed by German neuropsychiatrists in the nineteenth century. Although the occurrence of chronic psychoses of a schizophrenia-like nature in epilepsy has been reported in a number of studies in the recent era, the debate over the association between epilepsy and schizophrenia decelerated in the previous century, as the view on the relationship between these two disorders was altered from one of association to one of antagonism [4]. It was in the mid-twentieth century that the concept of the schizophrenia-like psychoses of epilepsy finally became explicit, which led to a resurgence of interest.

In the 1950s, Hill [5] briefly referred to the chronic paranoid hallucinatory psychoses with poor prognosis, which might develop in patients with epilepsy of temporal lobe origin. He mentioned that psychoses were likely to appear when the seizures had spontaneously ceased or became reduced in frequency by medication, and showed a gradual onset in early middle age while resembling a paranoid schizophrenic state. Pond [6] gave a more detailed description of the clinical features and noted that all had temporal lobe epilepsy with typical complex auras. The epileptic attacks usually began in the late teens and twenties, preceding the onset of psychotic symptoms for some years, with the latter often appearing to begin as seizures diminished in frequency. The psychotic symptoms included paranoid ideas that might become systematized, ideas of influence, auditory hallucinations that were often of a menacing quality, and occasional frank thought disorders with neologisms, condensed words, and inconsequential sentences. Furthermore, a religious coloring of the paranoid ideas was common. The affect tended to remain warm and appropriate, which was sometimes in contrast to ‘true’ schizophrenia, while there was also no typical ‘schizophrenic’ deterioration to an empty hebephrenic state.

Subsequently, Slater, Beard and Glithero published the epoch-making comprehensive series entitled “The schizophrenia-like psychoses of epilepsy: i to v” in 1963 and raised important clinical questions regarding psychoses of the schizophrenia-like nature asso-
associated with epilepsy [7-11]. Although some of those questions have been answered, many remain controversial.

Adequate recognition of psychoses in epilepsy is essential for physicians caring for affected patients, because the impact on their quality of life is too devastating to be overlooked. However, scant attention has been paid to this issue lately. Psychoses appear to be relatively uncommon among the psychiatric disorders that commonly accompany epilepsy, which is one reason for the recent diminishing trend of related studies [12-13]. On the other hand, the low incidence of psychoses in epilepsy may be more apparent than real, especially when mitigated forms of psychosis are taken into consideration.

In this review, current knowledge regarding schizophrenia-like psychoses of epilepsy is examined in light of the questions posed by Slater and colleagues.

2. Questions posed in “The schizophrenia-like psychoses of epilepsy”

The term “schizophrenia-like psychoses” was coined by Slater and colleagues and introduced in their series “The schizophrenia-like psychoses of epilepsy: i to v” [7-11]. The authors reported an uncontrolled fully descriptive study of 69 cases recruited from inpatients at two neuropsychiatric centers in London. All the patients had been diagnosed with epilepsy and later developed schizophrenia-like psychoses, and their psychotic state had persisted for weeks or months in a setting of apparently complete mental lucidity. Diagnosis of epilepsy was supported by electroencephalogram or unequivocal clinical evidence, and that of schizophrenia in most of the patients had been made by psychiatrists with experience. In some of the 69 cases, schizophrenia would have been the diagnosis of choice, according to the opinion of Slater and colleagues in the absence of a history of epilepsy.

The major questions posed in the series are listed by topic below and a review of each follows.

1. Epilepsy and schizophrenia as a chance combination
2. Epilepsy as a precipitating factor for schizophrenia
3. Symptomatology
4. Schizophrenia-like illness purely epileptic in origin
5. Possibility of heterogeneity
6. Pathogenesis of schizophrenia-like psychosis

2.1. Epilepsy and schizophrenia as a chance combination

Neither epilepsy nor schizophrenia is a rare disorder and occasional coincidence is to be expected. Slater et al. argued that the theory of chance combination of the two conditions was improbable based on epidemiological data. They made some empirical assumptions and calculated the annual incidence of
the chance combination to be four to five in
the whole London area. However, the fact
that they could so easily obtain 69 fresh cases
in 11 years from only two institutions among
many serving the same area convinced them
to abandon the theory of chance combination.
Their findings regarding indications of a pre-
disposition to schizophrenia, which their pa-
tients lacked and thus did not qualify as ‘true’
schizophrenics of the ordinary kind, also
played a supporting role in their decision. We
will discuss these indications later in suc-
ceding sections.

Many investigators have since supported
the conclusion of Slater and colleagues that
the association between epilepsy and schizo-
phrenia-like psychoses is more than coinci-
dental. On the other hand, some researchers
including Toone et al. [14] and Stevens [15]
were critical of Slater’s view of chance com-
bination. According to Stevens, the fact that
Slater and colleagues obtained 69 cases of
epilepsy and schizophrenia-like psychoses in
the greater London area was not remarkable,
as they were found among those referred for
epilepsy to prestigious neuropsychiatric referral
centers, where patients with epilepsy and
psychiatric disturbances were of special inter-
est to the neurosurgical staff during that peri-
od.

While a recent systematic review of pa-
pers published between 1965 through 2002
revealed 158 studies that generated a total of
1458 rates of schizophrenia [16], a survey
of earlier studies found few that reported inci-
dence of psychosis in epilepsy patients.
McGrath et al. [16] reported a median inci-
dence of schizophrenia of 15.2 per 100,000
individuals, whereas the reported incidence
of psychosis in epilepsy patients was a digit
greater. In a prospective study of interictal
psychoses of epilepsy, we previously report-
ed an average annual incidence of 0.42%
among adult epilepsy outpatients during a 56-
month study period [17]. Onuma et al. [18]
conducted a retrospective study of psychosis
in patients with epilepsy who visited their
adult epilepsy clinic between 1980 and 1994,
and found that the annual incidence of newly
developed psychosis varied from a minimum
of 0% to a maximum of 0.77%, with an aver-
age of 0.3%. Lindsay et al. [19] followed an
unselected sample of 100 children with lim-
bic seizures for more than a decade and found
that nine of 87 developed overt schizophreni-
iform psychosis in adult life, with an estima-
ed average annual incidence of approximately
0.75%. A national study in Denmark from
1977 to 1992 reported a 6.0% incidence of
psychiatric disorders that developed after a
diagnosis of epilepsy, or an average annual
incidence of 0.38% [20].

Direct comparisons of the above data are
difficult due to differences in the target popu-
lations and methodological diversity among
those studies. Nonetheless, they suggest that
a combined diagnosis of epilepsy with schiz-
ophrenia or schizophrenia-like psychoses due
to chance association alone would be unlike-
ly.

The prevalence of schizophrenia is rela-
tively high owing to the chronicity of the dis-
order. The median lifetime morbid risks for
males and females were reported to be 4.1
and 4.6, respectively, per 1000 individuals [16]. Gudmundsson [21] in his survey of 987 patients with epilepsy in Iceland noted that 5.5% of the males and 9.1% of the females were psychotic, and concluded that the frequency of psychosis was higher among individuals with epilepsy than in the general population, while citing the estimated expectancy of psychoses reported by Helgason [22]. Helgason [22] estimated the expectancy of developing psychoses up to the age of 61 years at 4.73% for males and 6.90% for females, compared with 0.57% and 0.90%, respectively, for schizophrenia.

Another example that supports the notion that coexistence of epilepsy and schizophrenia is more than a chance combination is the population-based cohort study conducted by Qin et al. [23]. They examined the risk of schizophrenia or schizophrenia-like psychosis associated with a history of epilepsy using data from Danish longitudinal registers. The cohort comprised approximately 2.27 million individuals, of whom 34,494 (1.5%) had a history of epilepsy. Among the epilepsy patients, 276 (0.8%) and 519 (1.5%) developed schizophrenia and schizophrenia-like psychosis, respectively, during the follow-up period. The authors concluded an increased risk of schizophrenia (relative risk 2.48, 95% confidence interval 2.20 to 2.80) and schizophrenia-like psychosis (relative risk 2.93, 95% confidence interval 2.69 to 3.20) in individuals with a history of epilepsy.

2.2. Epilepsy as a precipitating factor for schizophrenia

Slater and colleagues excluded the possibility of preexisting epilepsy being a precipitating factor for the development of schizophrenia in individuals genetically predisposed to the disorder, which might account for the combination of the two conditions, based on the following grounds. If the hypothesis of preexisting epilepsy predisposing to the development of schizophrenia is true, one would expect an increased incidence of schizoid traits in the prepsychotic personalities of patients and also an increased incidence of schizophrenia among their relatives. Their findings, however, did not support any of the above expectations. We will discuss the family history of psychoses in this section, while the prepsychotic personalities of epilepsy patients will be mentioned in the following section.

In a controlled study of psychosis with temporal lobe epilepsy, in which 50 patients with both epilepsy and psychoses and another 50 with only epilepsy were studied, Flor-Henry [24] confirmed the contention of Slater and colleagues that there was no genetic predisposition to psychosis. However, later studies of family history have found an increased incidence of psychotic episodes among relatives of epilepsy patients with psychosis.

Jensen [25] conducted a genetic investigation of 74 Danish patients with drug-resistant temporal lobe epilepsy who underwent a unilateral temporal lobectomy. His report revealed that 34 (45.9%) of those patients had a
family history of severe psychiatric disorders, with a total of 81 close relatives thus afflicted; and that a positive family history of a parent and/or sibling with major psychiatric disorders had an exceedingly unfavorable influence on the psychiatric status at follow-up. Among the 74 patients, 20 patients were psychotic [26]. Eleven patients suffered from psychoses preoperatively and an additional nine became psychotic in the postoperative follow-up period, including six after cessation of their epileptic seizures. Thirteen of those 20 psychotic patients (65%) had a family history of psychiatric disorders as compared to 21 (39%) of the remaining 54 non-psychotic patients [27].

Adachi et al. [28] reviewed the clinical data of 246 epilepsy patients with interictal psychosis and 658 control patients with epilepsy who had no history of psychotic episodes, and evaluated the variables for predicting the development of interictal psychosis in epilepsy. Patients with a positive family history of psychosis were found to be extremely susceptible to psychosis and the risk was nearly 40 times higher compared to patients without such family history.

In the population-based cohort study discussed in the previous section, Qin et al. [23] reported that a family history of psychosis was a significant risk factor for the development of schizophrenia or schizophrenia-like psychosis among individuals with a history of epilepsy, with relative risks of 7.57 (95% confidence interval 6.98 to 8.20) and 6.24 (5.83 to 6.69), respectively.

The above findings presented in recent studies suggest that a genetic factor plays an important role in the coexistence of epilepsy and psychoses. In other words, there appears to be an etiological relationship between epilepsy and psychoses.

2.3 Symptomatology

Slater and colleagues reported schizophrenic symptoms observed in their cases as follows:
- Delusion-formation of a typical schizophrenic kind in clear consciousness, e.g., mystical delusional experiences and delusions of persecution.
- Typically schizophrenic hallucinatory experiences in clear consciousness, e.g., auditory hallucinations, often with a menacing and persecutory quality.
- Thought disorder of schizophrenic type, e.g., thought blocking and neologisms.
- Affective disturbance, e.g., moods of depression, irritability, and aggressiveness, and flatness of affect.
- Impairment of volition and catatonic phenomena, e.g., reduction of energy, interest and initiative; impulsive and bizarre acts; and manneristic behaviour.

While all the cardinal features of schizophrenia were exhibited at some time by those patients, Slater and colleagues pointed out that the psychoses observed deviated from schizophrenic norms in some respects: affective responsiveness tended to be preserved to
an extent and a personality sometimes remained substantially undamaged even in the later stages of development of psychosis. With regard to premorbid personality, they stated that it was of the normal type with no evidence of schizoid traits in excess.

Their observations were presented in detail and the study is remarkable in many ways. However, it was not controlled, thus the conclusions remain open to questions and criticism. Some controlled studies have since been conducted, although they did not reach an agreement on the symptomatological issues between ‘true’ schizophrenia and schizophrenia-like psychoses of epilepsy.

Perez and Trimble [29] decided to use rating scales instead of subjective descriptive criteria to compare the diagnoses of epileptic psychosis and process schizophrenia in their prospective study. Using the Present State Examination (PSE), a standardized and structured psychiatric interview, and CATEGO, a computerized diagnostic classification program, for the diagnosis of psychoses, they compared 23 epilepsy patients with active psychosis under clear consciousness and 10 patients diagnosed with process schizophrenia. They pointed out the heterogeneous nature of psychoses in epilepsy and gave special emphasis on the affective components.

Toone et al. [14] retrospectively analyzed the clinical data of 69 epilepsy patients with psychoses and those of 53 control patients with a diagnosis of functional psychosis, using also the PSE and CATEGO. They found a relative absence of abnormal premorbid personality traits among epilepsy patients with schizophrenia-like psychoses. These patients experienced more delusions of reference and persecution, and showed fewer catatonic features compared to the patients with functional psychosis.

The First Rank Schneiderian Symptom Enquiry List adapted from the PSE was used in an investigation conducted by Oyebode and Davison [30] on the clinical characteristics and outcomes of epileptic schizophrenia. Thirty-two epilepsy patients with a diagnosis of schizophrenia were compared with 31 age-matched patients with a diagnosis of functional schizophrenia. They reported that the prevalence of each first-rank symptom studied was similar, except for delusions of passivity, which were experienced by 80% of the patients with functional schizophrenia and 34% of the patients with epilepsy and schizophrenia (P <0.0005). Third person auditory hallucinations were the most common type experienced by both groups.

Our previous study also revealed differences in symptom profiles between schizophrenia and psychoses in epilepsy [17]. We employed the Positive and Negative Syndrome Scale (PANSS) to assess psychotic symptoms and found that negative symptoms such as blunted affect were less apparent in epilepsy patients with psychoses.

On the other hand, Mace [31], in his critical review article on Slater’s work, pointed out that neither Toone et al. [14] nor Perez and Trimble [29] could validate the claimed absence of personality deterioration, and that
these phenomenological studies had failed to discriminate between schizophrenia and psychoses in epilepsy.

Furthermore, a multicenter study conducted in Japan reported contrasting results to the above-mentioned controlled studies: that the symptomatological difference between psychoses associated with epilepsy and schizophrenia is quantitative rather than qualitative [32]. Matsuura et al. [32] established the validity of the Japanese version of Operational Criteria Checklist for Psychotic Illness (J-OPCRIT) and adopted it to examine 58 consecutive patients with epileptic psychoses (index group) and age- and gender-matched patients with schizophrenia spectrum disorders (control group). An exploratory factor analysis identified five factor solutions of manic, negative, depressive, vegetative and positive symptoms. While the two groups shared a similar factor profile, the negative symptoms (such as blunted affect) and positive symptoms (such as third person auditory hallucinations) were less severe in the index group than in the control group.

Epilepsy is not a separate disease entity nor is idiopathic psychosis. An inevitable consequence is that psychoses associated with epilepsy are not homogeneous, but rather heterogeneous in nature [29, 33]. Nevertheless, even with knowledge of the heterogeneity of epileptic psychoses, the question of whether there is a fundamental difference in symptomatology between epileptic and idiopathic psychoses is yet to be answered.

2.4. Schizophrenia-like illness purely epileptic in origin

Now that a combined diagnosis of epilepsy with schizophrenia or schizophrenia-like psychoses due to chance association alone is considered to be unlikely, an etiological relationship of some kind is thought to exist between epilepsy and psychoses. Slater and colleagues asserted that there was no evidence against the view that the schizophrenia-like psychoses they observed were etiologically different from ordinary forms of schizophrenia and constituted a special kind of epileptic psychosis, although they initially stated that all of the patients in their study had been or would have been diagnosed with schizophrenia. They presented two views on the probable etiological relationship between the two conditions, which we shall discuss in turn. First, “the epilepsy itself, i.e. the occurrence of epileptic fits, could be the cause of the psychosis.” Second, “the basic disorder of function, which manifests itself in epileptic fits, could be the cause of the psychosis.”

2.4.1. Epilepsy itself could be the cause of the psychosis

To examine whether epilepsy per se may cause psychosis, the following variables would be good candidates for investigation: age at onset of epilepsy, duration of epilepsy, type of epilepsy, type of seizures, frequency of seizures, severity of seizures, and lateralization of epileptiform discharges.
Slater and colleagues reported a significant positive correlation of 0.58 between the ages of onset of epilepsy and schizophrenia, with a mean interval of 14 years, and they concluded that the duration of epilepsy was likely to be one of the causative factors. Many of their patients were found to suffer from seizures of temporal lobe origin, thus they stated that an etiological relationship might exist between the epileptic seizures of temporal lobe origin and psychosis.

In the above-mentioned controlled investigation, Flor-Henry [24] asserted that temporal epilepsy was etiologically associated with schizophrenic forms of epileptic psychoses and that “epileptic psychoses are fundamentally related to the epileptic process rather than non-specific psychoses resulting from structural brain damage”. Furthermore, contrast to Slater’s findings, he asserted that the duration of epilepsy or the age at onset did not appear to play a role in the development of psychoses in temporal lobe epilepsy. The absence of a control group in the series of Slater and colleagues was attributed to the differences in conclusion over the duration of epilepsy and presence of organic brain damage being etiologically relevant factors.

With regard to age at onset of epilepsy in epileptic psychoses, several controlled investigations are available for comparison. While the first two of the studies discussed below dealt with only temporal lobe epilepsy, the others did not restrict their subjects to a particular type of epilepsy.

In a controlled study of 198 epilepsy patients having partial seizures with complex symptoms, one-half of whom had paranoid/hallucinatory psychosis under a state of clear consciousness and the other half had no psychosis, Kristensen and Sindrup [34] reported no significant difference in the median age at onset of epilepsy or duration of epilepsy at the time of examination between the two groups. Sengoku et al. [35] carried out a comparative study of 96 patients with temporal lobe epilepsy, 48 of whom were psychotic and 48 were not, using inclusion criteria similar to those of Kristensen and Sindrup. The two groups in their study did not show a significant difference in mean age at onset of seizures.

On the other hand, Adachi et al. [28] reported that age at onset of epilepsy was one of the most important predictors for the development of interictal psychosis, together with a family history of psychosis, type of seizures, and level of intelligence. In their study, patients with interictal psychosis had a significantly earlier age at onset of epilepsy. In addition, complex partial seizures or generalized tonic clonic seizures and borderline intellectual functioning were also found to be important predictors. Another controlled investigation also found that patients with schizophrenia-like psychosis had an earlier age at onset of epilepsy. Schmitz et al. [36] retrospectively investigated the role of psychosocial and biological risk factors for the development of psychiatric complications in epilepsy. Their data analysis suggested that a multifactorial etiological relationship existed...
between epilepsy and schizophreniform psychoses. Severe epilepsy involving the limbic system and an unfavorable familial background were also found to be risk factors.

Based on the findings of the above investigations, it appears questionable whether an earlier age at onset of epilepsy is a unique causative factor for the development of interictal schizophrenia-like psychoses. It is convincing that the etiological relationship between epilepsy and psychoses is not so simple, and that there are many mechanisms by which their association may be accounted for [37]. It is also likely that multiple factors coexist and interact with one another in each patient, and that the seizures modify the presentation of the psychosis and vice versa. Age at onset of epilepsy would be one of the important risk factors for epileptic psychoses. However, seizure type; namely complex partial seizures and generalized tonic clonic seizures, is likely to have a more direct and stronger association with psychoses. Investigations of the issues related to type of epilepsy, type of seizures, and lateralization of epileptiform discharges will be reviewed in greater detail in the following sections.

2.4.2. The basic disorder of function, which manifests itself in epileptic fits, could be the cause of the psychosis

Rather than epilepsy per se, the pathological processes causing epilepsy could also be the etiology of psychoses in epilepsy. Slater and colleagues found 11 cases (16%) with a history of moderate to severe head injury in their case material and inferred that brain damage could lead to temporal lobe epilepsy and may also cause psychoses later in life.

As mentioned above, Flor-Henry [24] was critical of Slater’s findings and claimed that structural cerebral damage had nothing to do with the emergence of psychosis. Other researchers, however, did not quite agree with his view. Taylor [38] found a negative correlation between chronic psychoses and mesial temporal sclerosis, as well as overrepresentation of hamartomas in resected specimens from 100 patients treated surgically for temporal lobe epilepsy. Later, he reported that the occurrence of schizophrenia-like psychosis was not random and that the risk of psychosis was related to age at onset of epilepsy, gender, affected side, handedness, and especially the nature of the lesion in the temporal lobe [39]. In his investigation of 255 patients who had undergone a temporal lobectomy for relief of intractable psychomotor epilepsy, all 47 patients who had “alien tissue,” i.e., small tumors, hamartomas, or focal dysplasia, in the resected temporal lobe were compared with another 41 patients who showed mesial temporal sclerosis in the resected lobe. Five percent of the mesial temporal sclerosis group and 23% of the alien tissue group were psychotic.

Jensen and Larsen [26] agreed that the presence of a focal abnormality, or “alien tissue,” predisposed patients with temporal lobe epilepsy to psychosis. Bruens [40] also found
that temporal and limbic lobe dysfunctions closely correlated with the majority of the psychoses in his case material, although he was uncertain whether they were fundamentally related to the epileptic process as Flor-Henry claimed. In their controlled investigation of psychomotor epilepsy and psychosis, Kristensen & Sindrup [34] argued that epileptic psychoses were truly organic and caused by structural cerebral damage to the deep limbic parts of the temporal lobe, which was responsible for both epilepsy and psychosis.

2.5. Possibility of heterogeneity

Perez and Trimble [29] suggested that psychoses associated with epilepsy were heterogeneous in nature, while Bruens [40] proposed a multifactorial causality and stated “the different factors being of different value in individual cases,” instead of postulating a simple pathogenesis of the psychotic states in epilepsy. Slater and colleagues, however, were less than enthusiastic about the possibility of heterogeneity in theory, which might account for the combination of schizophrenia-like psychosis with preexisting epilepsy. Nevertheless, they pointed out that inspecting the differences among the three clinical groups in their case material could provide a means of demonstrating heterogeneity. Phenomenological similarity in psychoses does not necessarily indicate that the underlying mechanism of development of psychoses is the same and it is highly probable that their case material was composed of different types of epileptic psychoses.

Heterogeneity can be viewed in light of differences in age at onset of psychosis, and Japanese researchers have drawn direct comparisons of age at onset of psychoses between schizophrenia, interictal psychoses, and postictal psychoses. Discrimination based on a chronological classification of epileptic psychoses has been widely used in observations of epilepsy, although each subcategorized entity shares some clinical features in common [33, 41].

Kanemoto et al. [42] investigated patients with postictal psychosis with the aim of comparing them to patients with acute interictal psychosis and those with chronic psychosis. The study included 30 patients with postictal psychosis, 33 with acute interictal psychoses, and 25 with chronic psychosis, with mean ages at onset of psychoses of 32.1, 28.0, and 25.8 years, respectively. All the patients in that study had either complex partial seizures or temporal epileptogenic foci in electroencephalographic findings. In our previous study, we reported that patients with schizophrenia had a significantly earlier age of onset of psychosis compared to epilepsy patients, with mean ages of 21.6 and 35.7 years, respectively ($p = 0.003$) [17]. In an investigation of the difference in age of onset of psychosis between epilepsy and schizophrenia, Adachi et al. [43] found that patients with epileptic psychoses experienced their first psychotic episode significantly later in life than schizophrenic patients ($p = 0.000$). A total of 282 epilepsy patients and 612 schizo-
phrenic patients were consecutively enrolled in that study. The authors found 36 postictal, 224 interictal, and 22 bimodal psychoses in the epilepsy patients, with mean ages of onset of psychoses in the three groups reported to be 37.4, 29.0, and 26.8 years, respectively. In the schizophrenic patients, the mean age of onset was 26.6 years. The results of these studies confirm that schizophrenia has the earliest onset and postictal psychosis the latest, with interictal psychosis in between, which suggests heterogeneity in psychoses associated with epilepsy.

2.6. Pathogenesis of schizophrenia-like psychosis

The introduction of electroencephalographic examinations into clinical practice has drawn attention to the association between psychopathology and temporal lobe abnormalities. In an analysis of 458 cases with electroencephalographic data, Gibbs [44] found that 95% of 163 cases with focal seizure activity in the anterior temporal lobe had clinical psychomotor seizures, and that a psychiatric disorder was more than three times more common in cases with focal seizure activity in the temporal lobe than in those with an extratemporal focus. He stated, “The psychiatric symptoms which accompany psychomotor epilepsy are clinically indistinguishable from those encountered in ‘purely psychiatric’ disorders.”

Many studies that followed the publications of Gibbs were in favor of his view: that an association exists between psychosis and temporal lobe epilepsy or complex partial seizures. On the other hand, some researchers have been cautious in interpreting the results of those reports. Stevens [15] concluded that a review of literature on relationships between epilepsy and schizophrenia did not find a greater incidence of schizophrenia among epilepsy patients nor of epilepsy in patients with schizophrenia. She also pointed out that there were serious problems in sampling and diagnosis of both epilepsy and psychopathology in studies on the incidence of psychiatric disorders in epilepsy. Obviously, a high incidence was found in surveys of epilepsy in hospitals or clinics specializing in the treatment of intractable seizure disorders, and a low incidence in community-based surveys. In a large-scale survey based on Danish longitudinal registers mentioned earlier, Qin et al. [23] found that the increased risk for schizophrenia or schizophrenia-like psychosis did not differ according to the type of epilepsy. In contrast, Kanemoto et al. [45] found a highly significant association between temporal lobe epilepsy and interictal psychotic states in their study conducted at the Kansai Regional Epilepsy Center, a referral institution in Japan. A total of 132 epilepsy patients with interictal psychotic episodes and another 2773 epilepsy patients with no history of psychotic episodes were included in their study. Temporal lobe epilepsy was diagnosed in 74 patients (56%) in the psychotic group and 455 (16%) in the non-psychotic group.

Stevens [46] claimed that better epidemi-
logic studies are required to determine whether temporal lobe epilepsy predisposes patients to psychosis. Nonetheless, she additionally stated that when epilepsy patients also had psychosis, those with temporal lobe epilepsy more frequently manifested symptoms characteristically associated with positive symptoms of schizophrenia, e.g., hallucinations, delusions, and paranoia, as compared to patients with generalized epilepsy.

It is important to note Mace’s [31] remarks that the designation of temporal lobe epilepsy is incomparable among various studies, as temporal lobe epilepsy and complex partial seizures had effectively been equated and used interchangeably across different reports. As an example, although frontal lobe seizures with complex symptomatology were recognized no later than the middle of the twentieth century [47], complex partial seizures of extratemporal origin have been frequently misdiagnosed [48]. On the other hand, the extratemporal origin of complex partial seizures has been increasingly recognized. Williamson and Spencer [48] found that approximately 30% of their patients exhibited complex partial seizures of extratemporal origin in their investigation with intracranial electrodes. In an assessment of psychiatric morbidity associated with epilepsy, Edoh and Toone [49] found that 48% of their 88 adult cases had psychiatric problems. They also reported that patients with focal non-temporal lobe epilepsy did not differ from those with temporal lobe epilepsy in terms of global severity of psychiatric disturbance, whereas the latter showed a greater prevalence of psychiatric morbidity. Adachi et al. [50] also stated that the location of epileptogenic focus did not appear to primarily affect the psychiatric features of patients with epilepsy, although they found that patients with frontal lobe epilepsy exhibited hebephrenic symptoms during the active phase of interictal psychosis, while patients with temporal lobe epilepsy tended to show paranoid symptoms. In their study on predictive variables of interictal psychosis of epilepsy, Adachi et al. [28] employed multivariate analysis that revealed seizure type (such as complex partial seizures) to be statistically more strongly associated with psychosis than epilepsy type (such as temporal lobe epilepsy).

With respect to seizure type, Adachi et al. [28] found a significantly higher frequency of complex partial seizures among patients with psychoses than those without psychoses. Schmitz and Wolf [51] also reported that ictal loss of consciousness, an indicator of widespread cerebral dysfunction, was a risk factor of psychosis in epilepsy, but not localized or lateralized cerebral lesion, in a large series of consecutive outpatient referrals with epilepsy. Sengoku et al. [35] found that the psychotic group in their case material exhibited generalized tonic-clonic convulsions and compound seizures at a significantly higher rate compared with the non-psychotic group. They suggested that generalizing mechanisms of temporal lobe epilepsy may play a significant role in the emergence of epileptic psychoses, on the basis of their findings as well
as the contention of Rodin et al. [52] that temporal lobe epilepsy patients with grand mal seizures were more prone to develop psychotic disturbances than those without grand mal seizures.

Lateralization of epileptiform discharges in electroencephalographic findings has attracted the attention of researchers since Flor-Henry [24] advocated its correlation with psychotic manifestations. He found three sets of factors that significantly correlated with psychosis in his case material: (1) temporal lobe epilepsy, (2) fewer or no psychomotor seizures, and (3) lateralized to or involving the dominant hemisphere. He also found “a significant trend suggesting that the more the dominant hemisphere is involved, the more schizophrenic is the psychosis and that non-hemisphere is associated with manic-depressive states.” The laterality issue is highly controversial and consensus has not been achieved. A recently reported magnetoencephalographic study by Fukao et al. [53] presented affirmative results. They examined a total of 57 epilepsy patients with temporal lobe origin, 16 of whom with a history of psychosis, to identify magnetoencephalographic characteristics of psychosis in patients with temporal lobe epilepsy. Their findings suggested that dysfunction of the left temporal neocortex specifically contributed to the manifestation of psychotic symptoms in patients with temporal lobe epilepsy.

Magnetoencephalography was also applied to investigate working memory deficits in chronic interictal epileptic psychosis and schizophrenia, which revealed a similar profile of functional cognitive abnormalities in both conditions [54]. A total of 12 epilepsy patients with chronic interictal psychosis, 14 patients with nonpsychotic epilepsy, 14 schizophrenia patients, and 14 healthy control subjects were included in this investigation. Canuet et al. [54] found a similar magnetoencephalographic pattern of right dorsolateral prefrontal cortex and left temporal functional abnormalities in epilepsy patients with psychosis and patients with schizophrenia during performance of a working memory task. Their findings support Flor-Henry’s view of a preponderance of left-sided pathology in patients with schizophrenia-like psychosis, in addition to the possibility of shared underlying pathophysiological mechanisms between epileptic psychoses and schizophrenia. Previous neuropsychological studies [55, 56] also presented results compatible with those of Canuet et al. [54]. The profile of cognitive impairment exhibited by epilepsy patients with schizophrenia-like psychosis resembled that of schizophrenia, although it was less pronounced. Executive dysfunction as well as memory impairment is a distinctive feature of cognitive decline observed in schizophrenia; thus temporal lobe dysfunction alone cannot provide an adequate explanation for their findings.

Sundram et al. [57] found not only significant grey and white matter deficits encompassing the medial temporal lobe structures, but also deficits extending to the lateral temporal and extratemporal regions, in temporal
lobe epilepsy patients with psychosis. Some of these deficits overlapped with those found in schizophrenia. A total of 20 patients with temporal lobe epilepsy, 10 of whom with psychosis and another 10 without a history of psychosis, were involved in this investigation. They were matched for age, gender, handedness, epilepsy duration, seizure laterality, severity of epilepsy, and anti-epileptic medication. All the participants underwent magnetic resonance imaging scanning, followed by voxel-based morphometry analyses of grey and white matter anatomy. The findings showed that deficits in patients without psychosis were mainly localized in the temporal lobe, whereas marked cortical, subcortical, and extratemporal bilateral grey and white matter deficits were found in patients with psychosis. These results suggest that widespread abnormalities in the brain lead to psychoses in patients with temporal lobe epilepsy, which may also explain the findings of Taylor [39] and Jensen and Larsen [26] that the presence of focal abnormality, or “alien tissue,” predisposes patients with temporal lobe epilepsy to psychosis.

3. Conclusion

Slater and colleagues stated that “the schizophrenia-like psychoses of epilepsy” were schizophrenic in form, but not in etiology, and that they were symptomatic schizophrenias. In the past half-century, we have obtained additional information about psychoses in patients with epilepsy. Nevertheless, it is questionable whether a significantly better understanding of schizoprophreniform psychoses associated with epilepsy has been gained. Epileptic psychoses are heterogeneous in nature. Multiple factors coexist and interact in the etiological relationship between psychoses and epilepsy; thus simple causal links between the two conditions cannot be postulated. Investigations with new advanced technology, especially in neurophysiological, neuroimaging, and genetic fields, appear to be capable of exploring the similarities and contrasts between psychoses with and without epilepsy. Nevertheless, at this time, the questions posed by Slater and colleagues remain to be answered.

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