



# Epilepsy and Schizophrenia: Association or Antagonism? Epilepsie et schizophrénie: association ou antagonisme?



Philippe Gélisse<sup>1</sup>, Arielle Crespel<sup>1</sup>, Pierre Genton<sup>2</sup>

1-Epilepsy Unit, Gui De Chauliac Hospital, Montpellier (France)

2-Centre Saint Paul et Henri Gastaut Centre, Marseille (France)

Email : p\_gelisse@hotmail.com

No disclosure to declare.

## Abstract

The relationship between epilepsy and schizophrenia is complex. In 1934, von Meduna proposed camphor-induced convulsions in the treatment of schizophrenia and concluded that there was a biological antagonism between epilepsy and schizophrenia. From the 1950s on, the prevalence of psychosis in epileptic patients has been studied repeatedly. The work of Slater et al. (1969) had a profound impact. Over a few years, they collected 69 cases of inter-ictal psychosis (schizophrenia-like psychosis) among epileptics. The onset of seizures preceded the development of mental deterioration by an interval of several years. Temporal lobe epilepsy was over-represented. Although the patients exhibited at times all the cardinal features of schizophrenia, the psychoses observed deviated from schizophrenic norms in some respects. Conversely, the occurrence of seizures and/or epilepsy in schizophrenics was documented many years ago and was not considered a major problem. Using modern diagnostic criteria of schizophrenia and epilepsy, Gélisse et al. (1999) confirmed that the prevalence of epilepsy and acute symptomatic seizures was low in schizophrenics, which points to a possible relative "resistance" to factors of epileptic seizures. In this article, we discuss the relationship between epilepsy and schizophrenia and hypothesize that there is an antagonism between seizures (not epilepsy) and schizophrenia. However, there is a link between longstanding and drug-resistant epilepsy and interictal psychosis, so epilepsy and schizophrenia-like psychosis can be associated.

**Keywords:** Epilepsy- Schizophrenia- Psychosis.

## Résumé

Les relations entre épilepsie et psychoses ont été le sujet de nombreuses discussions et controverses. En 1934, von Meduna proposa le camphre pour induire des crises convulsives dans le traitement de la schizophrénie et conclut qu'il y avait un antagonisme biologique entre l'épilepsie et la schizophrénie. Cependant, une association entre épilepsie et psychoses a été évoquée au début du siècle mais avec de considérables incertitudes. A partir des années 1950, de nombreux travaux ont été consacrés à ce sujet. Les psychoses schizophréniformes de l'épilepsie (schizophrenia-like psychosis des auteurs anglo-saxons) se développeraient au bout de plusieurs années d'évolution d'une épilepsie temporale mal contrôlée. La prévalence s'échelonne de 0,74 % à 9,25 %. Des différences culturelles et d'époque quant à la définition de la schizophrénie et de l'épilepsie temporelle explique

en partie la variabilité des résultats. Beaucoup d'études ont fait l'objet de biais méthodologiques en considérant l'épilepsie temporelle comme un syndrome homogène décrit à l'époque comme épilepsie « psychomotrice » mais aussi en présélectionnant des populations de malades épileptiques graves consultant des centres spécialisés. C'est ainsi que Slater et al. (1969) concluaient à une relation en trouvant une fréquence de survenue d'une psychose schizophréniforme supérieure à celle de la population générale. Le début des crises précédait le développement d'une psychose de plusieurs années. Les épilepsies temporelles « psychomotrices » étaient surreprésentées. Slater et al. (1963) avaient remarqué que si tous leurs patients avaient présenté à un moment ou à un autre, un des signes cardinaux de la schizophrénie, leur tableau ne correspondait pas à une vraie schizophrénie. Une histoire familiale de schizophrénie et une personnalité schizoïde prémorbide étaient relativement rares dans leur population. Cette opinion que ces patients ne présentent pas une schizophrénie typique est partagée par d'autres auteurs. Inversement, la survenue de crises ou d'une épilepsie chez des patients schizophrènes n'a jamais été considérée comme un véritable problème. En utilisant des critères modernes de diagnostic de schizophrénie et d'épilepsie, Gélisse et al. (1999) ont confirmé que la prévalence de l'épilepsie et des crises symptomatiques aiguës étaient rares chez ces patients et ceux malgré l'utilisation de psychotropes. Dans cet article, nous discutons les relations entre épilepsie et schizophrénie. Nous émettons l'hypothèse qu'il y a un antagonisme entre les crises d'épilepsie et la schizophrénie. Cependant, il y a un lien entre une épilepsie pharmacorésistante évoluant depuis de nombreuses années et une psychose schizophréniforme intercritique, ainsi schizophrénie (schizophrenia like-psychosis) et épilepsie peuvent être associées.

**Mots clés :** Epilepsie- Schizophrénie- Psychose.

## Introduction

Epilepsy is a condition characterized by the recurrence of unprovoked seizures. Schizophrenia is a serious mental illness in which a person may lose contact with reality and experience hallucinations and delusions among other symptoms. Both epilepsy and schizophrenia are chronic disorders. The relationship between these two diseases is still controversial. In 1934, von Meduna proposed camphor-induced convulsions in the treatment of schizophrenia: as convulsions appeared to alleviate

the symptoms of psychosis, he concluded that there was a biological antagonism between the two conditions [1]. Conversely, patients with long-standing epilepsy develop schizophrenia-like psychosis at a rate exceeding that expected if the two disorders were independent [2]. Schizophrenia-like psychosis means that patients do not show a typical schizophrenic deterioration. It can be differentiated from schizophrenia in term of phenomenology, course, and outcome [3]. This is possibly the core of the controversy between antagonism or association between epilepsy and schizophrenia. We will here discuss the problem of epilepsy occurring in patients with schizophrenia and the reverse problem, i. e. epilepsy preceding and/or causing schizophrenia.

### Epilepsy in Schizophrenia

The occurrence of seizures and/or epilepsy in patients with a chronic schizophrenia was documented many years ago and was not considered a major problem. In 1931, Glaus found only eight cases of epilepsy among 6,000 schizophrenic patients and stated that "schizophrenia has but a very slight pathogenetic significance for the outbreak of epileptic attacks" [4]. In 1932, Steiner and Strauss found 20 patients with seizures among 6,000 schizophrenics [5]. They wrote: "we find in only 20 cases anything regarding seizures either in the history, or during clinical observation, or in the follow-up. Typical epileptiform seizures are, if they occur at all, so very rare in true schizophrenia, that they immediately raise doubts about the correctness of the psychiatric diagnosis". Other epidemiological studies confirmed these results. They were summarized by Davison and Bagley (1969) (Table I) [6].

**Table I: Prevalence of epilepsy in patients with schizophrenia, literature data (adapted from Davison and Bagley, 1969) [6] - SE for confidence interval 95 %.**

Authors	Year published	No. of Schizophrenic Patients	No. with Epilepsy	% ± SE
Urstein	1909	200 (females)	39	195 ± 28
		100 (males)	14	80 ± 27
		2700	95	35 ± 3.5
Giese	1914	347	30	86 ± 15
Vorkastner	1918	217	10	46 ± 14
Krapf	1928	1506	18	12 ± 3
Glaus	1931	6000	8	1.3 ± 0.5
Seiner & Straus	1932	6000	20	3 ± 0.7
Kat	1937	50 000	145-165	3 ± 0.2
Esser	1938	552	11	20 ± 13.3
Yde et al.	1941	715	20	27 ± 6
Hoch	1943	500	2	4 ± 3
de Boor	1948	3242	2	0.6 ± 0.4
Smorto and Sciortra	1955	537	3	3 ± 3
Persic	1956	1827	14	7.7 ± 2
Ballerini and Laszlo	1964	665	13	20 ± 5
Mäkikyrö et al.	1998	89	4	45 ± 22

The early German figures are probably an over-estimation, because they probably included non-epileptic attacks [7-9]. From the 1920s, prevalence figures have repeatedly been reported as low, ranging between 0.06 and 2.7 percent [4, 5, 10-18]. These earlier studies were done prior to the current classification systems of psychiatric disorders and of epilepsies. They may have taken into account only the "convulsive" forms of epilepsy. They were generally based on institutionalized patients, and performed before the era of neuroleptic drugs. Mäkikyrö et al. (1998) reported a prevalence of epilepsy of 4.5 percent among chronically hospitalized schizophrenics, but the population studied was very small (89 patients) [19].

We performed an epidemiological study to assess the prevalence of seizure and epilepsy in a population-based group of patients diagnosed with schizophrenia or paranoid disorders according to DSM III-R (American Psychiatric Association, 1987) (DSM III-R 295 and 297.1, respectively) [20]. In France, mental health care has been organized by geographical zones called "sectors". In a well-defined territory and for a population of approximately 60,000 to 70,000 inhabitants, one single health team is in charge of the totality of the mentally ill. This team has the obligation to treat patients domiciled in its geographical zone. A patient can however freely choose a physician or a private psychiatric institution outside the sector if his mental state allows him to decide. Concerning chronic and serious psychiatric conditions, the psychiatric sector collects the essentials of such patients. A survey in a urban sector of Marseilles (France) that includes 56,910 inhabitants, collected 1,154 cases treated for psychiatric disorders, including 460 for schizophrenia or paranoid disorder. All 460 patients were on chronic neuroleptic treatment. Five had epilepsy (prevalence: 10.8 per thousand): cryptogenic temporal lobe epilepsy (2 cases), cryptogenic frontal lobe epilepsy (1 case), idiopathic generalized epilepsy (1 case) and chronic alcohol-induced epilepsy (1 case). Five were diagnosed with acute symptomatic seizures (prevalence: 10.8 per thousand), which appears as very few, given the accumulation of risk factors in schizophrenics: neuroleptic treatment, misuse of psychotropic drugs and repeated withdrawals, use of illicit drugs or alcohol. We wrote that "there is apparently no relationship between schizophrenia and paranoid disorders (DSM III-R 295 and 297.1) and epilepsy, and their occurrence together in a given patient is probably due to a coincidence". We also concluded that schizophrenia may be protective against seizure: « acute symptomatic seizure are not common in this population, in spite of multiple risk factors: their rarity in patients with schizophrenia may point to a possible, relative "resistance" to factors of epileptic seizures in patients with schizophrenia ».

### Schizophrenia in Epilepsy

Epileptic patients with temporal lobe epilepsy may develop schizophrenia. The occurrence of psychosis and/or schizophrenia has been studied repeatedly from the 1950s on. Most series suggest that the prevalence of schizophrenia-like psychosis in epileptic patients is higher than the general population. However, there is

a fundamental controversy in the literature about the frequency of schizophrenia in epileptics: between 0.74 to 9.25 percent [6, 21-29]. Table II summarized the main studies. Cultural and time differences explain in part the variability of the results.

**Table II: Prevalence of schizophrenia-like psychosis in epilepsy .**

Authors	Year published	No. with epilepsy	Prevalence
Alström	1950	897	0.8%
Bartlett	1957	1073	0.74%
Asuni & Pillutla	1967	42	26%
Davison & Bagley	1969	8572	0.7%
Bruens	1971	720	2.4%
Standage	1972	53	11.3%
Shukla	1979	132	10.6%
Edeh & Toone	1987	88	1.1%
Mendez et al.	1993	1611	9.25%
David et al.	1995	151	0%

Many studies were limited by both their methodology and their imprecise terminology. Many studies were performed in patients with serious epileptic conditions or consulting specialized centers for epilepsy or mental hospitals. Thus, over a period of eleven years, Slater et al. (1963) collected 69 cases of inter-ictal psychosis among epileptics in an English mental hospital [2]. For them, schizophrenia-like psychosis occurs more commonly than chance would predict. Their work had a profound impact. However, it was criticized for drawing conclusions on the basis of insufficient statistics [30].

Mendez et al. (1993) performed a study using the DSM III-R criteria for schizophrenia (American Psychiatric Association, 1987) [28]. Interictal psychosis occurred in 149 of 1,611 epilepsy outpatients (9.25 percent), but in only 23 of 2,167 (1.06 percent) outpatient migraine sufferers of a university medical center. This study has been criticized because it would have been better to compare epileptic subjects with a group of CNS-damaged patients, such as in multiple sclerosis [31]. David et al. (1995) investigated the incidence of schizophrenia in a cohort of 50 087 male Swedish conscripts [29]. At the time of conscription, there were 151 epileptic patients. The Swedish National Register of Psychiatric Care detected over 13 years 203 subjects admitted for schizophrenia and 197 for another type of psychosis. Of the 151 epileptic patients, two became psychotic (1.32 percent) but no schizophrenia was detected. This study can be criticized because of the small number of epileptic subjects. However, on the basis of the findings of Mendez et al., a greater number of schizophrenics

should have been detected. Another criticism is that about three percent of the male population had been excluded of conscription because of physical or mental deficiencies, thus patients with serious epilepsy, those precisely at risk for psychosis, may have been missed. Thus, in spite of modern studies, major doubts about the true prevalence of psychosis in patients with epilepsy do persist.

Schizophrenia-like psychosis observed in patients with epilepsy tends to have a relatively short and benign course [32]. Paranoid personality and schizotypal personality disorders are the most usual whereas negative symptoms are rare. Paranoid persons are suspicious. They present auditory hallucinations with interpretative ideas. They think that others want to harm, to poison them. As there is no systematization of the delirium in the majority of cases, this is not a paranoid disorder. Schizotypal personality corresponds to schizophrenia-like psychosis. Affective responsiveness tends to be preserved. Patients have a high frequency of delusions or hallucinations and religious mystical experiences. They have no formal thought disorder. Pond gave a precise description of the different clinical features in 1957: "they include paranoid ideas which may become systematised, ideas of influence, auditory hallucinations often of a menacing quality, and occasional frank thought disorders with neologism, condensed words and inconsequential sentences...a religious colouring of the paranoid ideas is common. The affect tends to remain warm and appropriate, which is sometime in contrast to 'true schizophrenia', nor is there typical 'schizophrenic' deterioration to the empty hebephrenic state" [33]. Indeed, the schizophrenia-like psychosis of epilepsy substantially differs from true schizophrenia. In their population of schizophrenic epileptic patients, Slater et al. noted that if the subjects have shown at times all cardinal features of schizophrenia, the psychoses observed deviate from schizophrenic norms in some interesting respects. "In summary one may say that there is not one of the cardinal symptoms of schizophrenia which has not been at some time exhibited by these patients. However, the combination of symptoms shown by individuals differs slightly from the most usual schizophrenic patterns. Although they are seen, catatonic phenomena of any gross degree are unusual, and loss of affective response does not occur so early or become so marked in the great majority of these patients as in the typical schizophrenic. By and large they are friendlier and more co-operative, and less suspicious of hospital staffs, so that only very rarely do they cause a serious nursing problem" [2]. A family history of schizophrenia and prepsychotic personalities was relatively rare in their population. The point of view that epileptic patients do not present a typical schizophrenia is shared by Bruens (1974) [34].

Seizures start in adolescence. Onset of epilepsy precedes the development of mental deterioration by an interval of several years (10-15 years). Drugs resistance, a history of status epilepticus, complex partial seizures, several types of seizures appear as risk factors for psychosis [35]. Most series report a higher frequency of psychosis in patients with focal than with generalized epilepsy [2, 26,

34]. Gibbs et al. (1948) wrote that “ a patient bearing the diagnosis ‘epileptic with psychosis’ is almost invariably a psychomotor epileptic” [36]. However, earlier studies were performed at a time where anatomical correlations were not well known. When a patient experienced loss of consciousness, it was labeled a psychomotor epilepsy. Nevertheless, there is a consensus that temporal lobe epilepsy is over-represented.

Flor-Henry (1969) and latter Sherwin (1981) found that epileptic patients with schizophrenia-like psychosis were more likely to have dominant hemisphere temporal lobe foci [37, 38]. This opinion is very controversial. Controlled studies did not find evidence of lateral predominance of the epileptogenic zone [26, 28, 39, 40]. Mendez et al. (1993) reported in their population 34 patients with an interictal focus on the left side, 29 on the right and 29 with a bitemporal interictal focus [28]. They then compared 62 epilepsy-with-schizophrenia patients with 62 epileptic patients without schizophrenia. They found no difference in the laterality of the epilepsy and on the anticonvulsant treatment. There were significant differences in age at onset of epilepsy (it was later in the first group), there were more complex partial seizures, more “auras” and more seizures. For these authors, the repetition of seizures in the temporo-limbic structures is one of the main elements provoking schizophrenia-like psychosis. Adachi et al. (2000) compared 246 patients with epilepsy and interictal psychosis and 658 control epileptic patients [41]. For these authors an earlier age at onset of epilepsy, complex partial seizures or generalized tonic clonic seizures, and borderline intellectual functioning were the most important predictors of interictal psychosis. In contrast to the opinion expressed by Slater et al., they also found a high frequency of family history of psychosis. Sex, a family history of epilepsy and the lateralization of epileptiform discharge did not correlated with psychosis. The frequency of seizures is a controversial element. Seizure activity is reported to be lower in psychotic patients than in non-psychotic patients, which is coherent with the hypothesis of alternance between psychosis and epilepsy. From his extensive review of the medical literature, Trimble (1991) wrote “while acknowledging assessment of seizure frequency is difficult, particularly retrospectively,..., the controlled studies both suggest a diminished frequency of psychomotor temporal lobe seizures in patients developing psychosis...This may be viewed as a form of antagonism between seizures and psychosis, a variant of the phenomena described by Landolt, as in some cases the EEG is shown to normalise” [35].

### **Conclusion**

Electroconvulsive therapy appeared in the past as an effective treatment of schizophrenia. Schizophrenic patients are not particularly prone to seizures. Schizophrenia may be protective against seizure. Schizophrenia-like psychosis appears when epileptic activity diminishes. It can thus be stated that there is apparently an antagonism between seizures (not epilepsy) and schizophrenia. However, there is a significant association between longstanding and

drug-resistant epilepsy and interictal psychosis: this, on the other hand, shows that epilepsy and schizophrenia (schizophrenia-like psychosis) are linked to some degree.

### **References**

- 1-Meduna LV. Versuche über die biologische Beeinflussung des Ablaufs der Schizophrenie. *Ztschr Neurol Psychiat* 1935; 152: 235-62.
- 2-Slater E, Beard AW, Glithero E. The schizophrenia-like psychoses of epilepsy. *Br J Psychiat* 1963; 109: 95-150.
- 3-Torta R, Keller R. Behavioral, psychotic, and anxiety disorders in epilepsy: etiology, clinical features, and therapeutic implication. *Epilepsia* 1999; 40 (Suppl. 10): 2-20.
- 4-Glaus A. Über Kombinationen von Schizophrenie und Epilepsie. *Ztschr Neurol Psychiat* 1931; 135: 450-500.
- 5-Steiner G, Strauss A. Die körperlichen Erscheinungen. In: Bumke O., ed. *Handbuch der Geisteskrankheiten*. Vol 9. Berlin: Springer, 1932.
- 6-Davison K, Bagley CR. Schizophrenia-like psychoses associated with organic disorders of the central nervous system: a review of the literature. In: Herrington RN, ed. *Current problems in neuropsychiatry*. Kent: Headley Brothers 1969; 133-84.
- 7-Urstein M. *Die Dementia Praecox und ihre Stellung zum Manisch-depressiven Irresein*. Berlin: Urban and Schwarzenburg, 1909.
- 8-Giese H. Über klinische Beziehungen zwischen Epilepsie und Schizophrenie. (Epilepsie als Frühsymptom oder als Kombination). *Ztschr Neurol Psychiat* 1914; 26: 22-112.
- 9-Vorkastner W. *Epilepsie und Dementia Praecox*. Berlin: Karger, 1918.
- 10-Krapf E. Epilepsie und Schizophrenie. *Arch Psychiat Nervenkr* 1928; 83: 547-86.
- 11-Kat W. Über den Gegensatz Epilepsie-Schizophrenie und das kombinierte Vorkommen dieser Krankheitsarten. *Psychiat Bl* 1937; 41: 733-45.
- 12-Esser PH. Die Epileptiformen Anfälle der Schizophrenen und die differentialdiagnostischen Schwierigkeiten im Grenzgebiet von Epilepsie und Schizophrenie. *Ztschr Neurol Psychiat* 1938; 162: 1-24.
- 13-Yde A, Lohse E, Faurbye A. On the relation between schizophrenia, epilepsy and induced convulsions. *Acta Psychiatr Scand* 1941; 16: 325-88.
- 14-Hoch P. Clinical and biological interrelations between schizophrenia and epilepsy. *Am J Psychiatry* 1943; 99: 507-12.
- 15-De Boer W. Zur Frage der Kombination von genuiner Epilepsie mit Schizophrenie. *Nervenarzt* 1948; 19: 279-85.
- 16-Smorto G, Sciorta A. Sul concetto di ‘antagonismo’ tra epilessia e schizofrenia. *Pisani* 1955; 69: 25-47.
- 17-Persic N. An observation on the relation between epilepsy and schizophrenia. *Neuropsihijatrija* 1956; 4: 263-74.
- 18-Ballerini A, Laszlo P. Considerazioni sull’associazione fra sindromi schizofreniche ed epilettiche rilevata sull’attuale popolazione degli O.P. di Firenze. *Rass Studi Psychiat* 1964; 53: 266-74.
- 19-Mäkikyrö T, Karvonen JT, Hakko H et al. Comorbidity of hospital-treated psychiatric and physical disorders with special reference to schizophrenia: a 28 year follow-up of the 1966 Northern Finland general population birth cohort. *Public Health* 1998; 112: 221-28.
- 20-Gelisse P, Samuelian JC, Genton P. Is schizophrenia a risk

factor for epilepsy or acute symptomatic seizures? *Epilepsia* 1999; 40: 1566-71.

21-Alström CH. A study of epilepsy in its clinical, social and genetic aspects. *Acta Psychiat et Neurol* 1950; 63 (suppl.): 284 Letter.

22-Bartlett J. Chronic psychosis following epilepsy. *Am J Psychiat* 1957; 114: 338-43.

23-Asuni T, Pillutla VS. Schizophrenia-like psychoses in nigerian epileptics. *Brit J Psy* 1967; 113: 1375-9.

24-Bruens JH. Psychoses in epilepsy. *Psychiat Neurol Neurochir* 1971; 74: 175-92.

25-Standage KF. Schizophreniform psychosis among epileptics in a mental hospital. *Brit J Psy* 1972; 123: 231-2.

26-Shukla GD, Srivastava ON, Katiyar BC, et al. Psychiatric manifestations in temporal lobe epilepsy. A controlled study. *Br J Psychiatry* 1979; 135: 411-7.

27-Edeh J, Toone B. Relationship between interictal psychopathology and the type of epilepsy. *Brit J Psy* 1987; 151: 95-101.

28-Mendez MF, Grau R, Doss RC, Taylor JL. Schizophrenia in epilepsy: seizure and psychosis variables. *Neurology* 1993; 43: 1073-7.

29-David A, Malmberg A, Lewis G, Brandt L, Allebeck P. Are there neurological and sensory risk factors for schizophrenia? *Schizo Res* 1995; 14: 247-51.

30-Stevens JR. Psychiatric implications of psychomotor epilepsy. *Arch Gen Psychiatry* 1966; 14: 461-71.

31-Stevens JR. Seizures and Psychosis. *Neurology* 1994; 44: 364-5.

32-Blumberg HP, Kanwal GS, Relkin N, Mattis S, Viederman M, Makari GJ. Psychiatric complications in a patient with complex partial seizures. *Am J Psychiatry* 1996; 153: 404-9.

33-Pond DA. Psychiatric aspect of epilepsy. *Journal of the Indian Medical Profession* 1957; 3: 1441-51.

34-Bruens JH. Psychoses in epilepsy. In: Vinken PJ, Bruyn SW, eds. *Handbook of clinical neurology*. Amsterdam: North Holland Publishing Company 1974; 15: 595-610.

35-Trimble MR. *The psychoses of epilepsy*. New York: Raven Press, 1991.

36-Gibbs FA, Gibbs EL, Fuster B. Psychomotor epilepsy. *Arch Neurol Psychiatr* 1948; 60: 331-9.

37-Flor Henry P. Psychosis and temporal lobe epilepsy. *Epilepsia* 1969; 10: 363-95.

38-Sherwin I. Psychosis associated with epilepsy. Significance of laterality of the epileptogenic lesion. *J Neurol Neurosurg Psychiatry* 1981; 44: 83-5.

39-Dongier S. Statistical study of clinical and electroencephalographic manifestations of 536 psychotic episodes occurring in 516 epileptics between clinical seizures. *Epilepsia* 1959; 1: 117-42.

40-Kristensen O, Sindrup HH. Psychomotor epilepsy and psychosis. *Acta Neurol Scand* 1978; 57: 361-79.

41-Adachi N, Matsuura M, Okubo Y et al. Predictive variables of interictal psychosis in epilepsy. *Neurology* 2000; 55: 1310-4.