

SHORT REPORT

Epileptic psychoses and anticonvulsant drug treatment

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Abstract

Forty four consecutive patients with epilepsy and psychoses were studied retrospectively for psychotic episodes associated with changes in antiepileptic drug therapy. Twenty seven patients (61%) developed their first episode of psychosis unrelated to changes in their antiepileptic drug regimen. Twenty three of these patients developed psychoses with temporally unrelated changes in seizure frequency. Many patients had chronic schizophrenia-like psychotic symptoms. Seventeen patients (39%) developed their first episode of psychosis in association with changes in their antiepileptic drug regimen. Twelve patients developed psychoses temporally related to seizure attenuation or aggravation. Many of their psychotic symptoms were polymorphic with a single episode or recurrent episodes. No marked differences were found in the various clinical backgrounds between the two groups. In the drug-related group, seven patients developed psychoses after starting add-on therapy with a new antiepileptic drug, six after abruptly discontinuing their drugs, and four after taking an overdose of antiepileptic drugs. Based on the present findings, drug regimens should be changed gradually and compliance should be maintained to prevent epileptic psychoses.

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Keywords: epilepsy; psychoses; anticonvulsant drug; risk factor

During antiepileptic drug therapy for epilepsy, some patients exhibit psychotic symptoms under clear consciousness. As only a minority of patients with epilepsy develop psychoses, attempts have been made to define the associated risk factors. Three main factors—epilepsy related variables, underlying brain damage, and psychosocial disadvantages—are thought to be important in the precipitation of epileptic psychoses. Lennox¹ first suggested that antiepileptic drug therapy is a cause of mental decay in 1942. However, it was not until the 1970s that serious attention was paid to medication as a factor in the genesis of psychoses.² The present study investigates the relation between the development of the first psychotic episode and

changes in the antiepileptic drug regimen, and proposes interventions which could prevent the development of psychoses in epileptic patients.

Subjects and methods

Forty four consecutive epileptic patients (20 male, 24 female), who presented with or reported psychotic symptoms under clear consciousness served as subjects for this retrospective study. The psychotic symptoms consisted of hallucinations, delusions, or a limited number of several abnormalities of behaviour, such as gross excitement and overactivity, marked psychomotor retardation, and catatonic behaviour as defined by the ICD-10 classification of mental and behavioural disorders.³ These patients were managed on an inpatient or outpatient basis by me from 1975 to 1997 at Nihon University School of Medicine. Twenty nine patients were referred to the neuropsychiatric department at the time of their first psychotic episode, and three were referred several years after the onset of their psychoses. Detailed reports about medication changes were received from the hospitals which referred patients. The remaining 12 patients developed their first psychoses during epilepsy management in the department. The follow up period was from 2 to 22 years, with an average of 11.1 years.

The patients were divided into two groups based on the presence or absence of changes in their drug regimen before the onset of the first episode of psychosis. One group did not undergo any anticonvulsant drug regimen changes before the development of psychoses (drug unrelated group, n=27), while the other had drug regimen alterations (drug-related group, n=17). The second group was divided into three subgroups: (1) psychoses developed after starting add on therapy with a new antiepileptic drug (add-on subgroup, n=7); (2) psychoses developed after the patients voluntarily and abruptly discontinued their antiepileptic drugs (discontinuation subgroup, n=6); and (3) psychoses developed after the patients deliberately took an overdose of antiepileptic drugs (overdose subgroup, n=4).

Frequency data were compared using the χ^2 test or Fisher's exact probability test. Parametric data were compared by analysis of variance (ANOVA).

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Drug-unrelated and drug-related psychoses

| | Drug-unrelated Group | Drug-related Group | Subgroups | | |
|---------------------------------------|----------------------|--------------------|------------|-----------------|-------------|
| | | | Add-on | Discontinuation | Overdose |
| Number of patients | 27 | 17 | 7 | 6 | 4 |
| Age*4: (y: mean (SD)) | 40.6 (14.4) | 41.5 (13.1) | 35.7 (7.6) | 52.7 (14.9) | 34.8 (6.2) |
| Sex: male, female | 11, 16 | 9, 8 | 3, 4 | 2, 4 | 4, 0 |
| Onset of epilepsy (y: mean (SD)) | 12.6 (9.5) | 14.2 (9.7) | 10.3 (9.7) | 19.2 (10.5) | 13.5 (6.8) |
| Onset of psychoses, (y: mean (SD)) | 27.9 (8.8) | 33.2 (10.4) | 29.3 (7.5) | 40.2 (12.2) | 29.5 (7.9) |
| Latency, years: mean (S.D.) | 15.2 (8.6) | 19.0 (11.8) | 19.0 (9.3) | 21.0 (16.2) | 16.0 (10.6) |
| Relation with epileptic seizures*1,*4 | | | | | |
| No relation to seizure | 23 | 5 | 3 | 0 | 2 |
| Postictal | 3 | 5 | 0 | 4 | 1 |
| Parictal | 1 | 1 | 0 | 1 | 0 |
| Alternative | 0 | 6 | 4 | 1 | 1 |
| Type of psychosis*1,*4 | | | | | |
| Polymorphic psychosis | 2 | 8 | 1 | 6 | 1 |
| Delusional psychosis | 8 | 5 | 4 | 0 | 1 |
| Schizophrenia-like psychosis | 17 | 4 | 2 | 0 | 2 |
| Anticonvulsant drug content | | | | | |
| PHT | 18 | 8 | 2 | 4 | 2 |
| CBZ | 15 | 7 | 3 | 2 | 2 |
| PB | 12 | 9 | 2 | 5 | 2 |
| VPA*2 | 10 | 2 | 1 | 1 | 0 |
| ZNS*2,*4 | 6 | 9 | 6 | 1 | 2 |
| Others | 11 | 5 | 2 | 2 | 1 |
| Psychotropic drug use*3 | | | | | |
| Antipsychotics | 21 | 14 | 7 | 3 | 4 |
| Benzodiazepines | 4 | 0 | 0 | 3 | 0 |
| None | 2 | 0 | 0 | 0 | 0 |
| Psychotropic drug maintenance*1 | | | | | |
| Antipsychotics | 13 | 4 | 3 | 0 | 1 |
| Benzodiazepines | 4 | 0 | 0 | 0 | 0 |
| None | 10 | 13 | 4 | 6 | 3 |
| Clinical course*1 | | | | | |
| Single episode | 7 | 10 | 4 | 3 | 3 |
| Recurrent | 4 | 6 | 2 | 3 | 1 |
| Chronic | 16 | 1 | 1 | 0 | 0 |

*1 $p < 0.01$ (χ^2) between drug-unrelated and drug-related groups.

*2 $p < 0.05$ (χ^2) between drug-unrelated and drug-related groups.

*3 $p < 0.01$ (χ^2) among subgroups in drug-related group.

*4 $p < 0.05$ (ANOVA, χ^2) among subgroups in drug-related group.

PHT=phenytoin; CBZ=carbamazepine; PB=phenobarbital; VPA=valproic acid; ZNS=zonisamide.

Results

CLINICAL FEATURES OF THE DRUG-RELATED AND DRUG-UNRELATED GROUPS

There were no statistical differences in clinical backgrounds, including age, sex, age at onset of epilepsy, age at onset of first episode of psychoses, and latency from onset of epilepsy to onset of psychosis between the drug-unrelated and drug-related groups (table). The types of epilepsy and the seizure frequency at the time of the study did not differ between the two groups.

The temporal relations between the development of the first episode of psychoses and changes in seizure frequency differed significantly between the two groups. Only four out of the 27 patients (15%) in the drug-unrelated group developed psychoses in association with seizure changes. By contrast, 12 out of the 17 patients (71%) in the drug-related group developed psychoses with a temporal relation to seizures.

The main psychopathology also differed between the two groups. Delusions of persecution and auditory hallucinations were common in both groups, whereas visual hallucinations and hallucinatory bodily sensations were significantly more frequent in the drug-related group. Delusions of being influenced, of robbery, of grandiosity, and of jealousy were seen only in the drug-unrelated group. Misidentification of persons, delusions of possession, functional auditory hallucinations, and hypochondriacal delusion were found only in patients in the drug-related group.

The types of psychoses differed significantly between groups, according to the ICD-10 classification. Schizophrenia-like psychosis was common in the drug-unrelated group, whereas polymorphic psychosis was common in the drug-related group. Delusional disorders occurred in both groups.

All patients except two were prescribed adjunctive psychotropic drugs in an active effort to treat their psychoses. Psychotropic drug use as maintenance therapy was significantly different between the two groups. Antipsychotic drugs, or benzodiazepines, or both were used in 17 out of 27 patients (63%) of the drug-unrelated group, but in only four out of 17 patients (24%) of the drug-related group.

The clinical course of the psychoses differed significantly between the two groups. Sixteen out of 27 patients (59%) of the drug-unrelated group followed a chronic clinical course, whereas 10 out of 17 patients (59%) of the drug-related group experienced only a single episode. Four patients (15%) of the drug-unrelated group and six patients (35%) of the drug-related group relapsed with psychoses between 1 month and 5 years after remission of their first psychotic episode. Six out of 10 relapsed patients did not receive any psychotropic drugs as maintenance therapy.

CLINICAL FEATURES OF THE THREE SUBGROUPS OF DRUG RELATED PSYCHOSES

The mean age of the discontinuation subgroup was significantly higher than that of the add-on

and overdose subgroups. However, there were no differences in sex, age of onset of epilepsy, age of onset of psychosis, and latency period from the onset of epilepsy to that of psychosis among the three subgroups.

The temporal relation with epileptic seizures was significantly different among the subgroups. Alternative psychosis was common in the add-on subgroup, and postictal psychosis was frequent in the discontinuation subgroup. The type of psychoses also differed significantly. Delusional psychosis was common in the add-on subgroup, all patients in the discontinuation subgroup developed polymorphic psychosis, and schizophrenia-like psychosis was frequent in the overdose subgroup.

Of the seven patients in the add-on subgroup, zonisamide was added as an adjunct to therapy with other antiepileptic drugs in six patients. Various drug combinations were administered to the patients in the discontinuation and overdose subgroups.

Psychotropic drug use for the adjunctive therapy differed significantly among the subgroups. All patients in the add-on and overdose subgroups were treated with antipsychotic drugs, whereas half of the patients in the discontinuation subgroup were treated with adjunctive benzodiazepines only. The clinical course did not differ among the subgroups.

Discussion

In the present study, the clinical backgrounds did not differ significantly between the drug-related and drug-unrelated groups. However, significant differences were found between the two groups in the genesis of psychoses and temporal relation with epileptic seizures, and the psychopathology and the type of psychoses.

Zonisamide, which most of the add-on subgroup had received as adjunctive therapy, is reported to be often related to psychoses in Japan.⁴ Ferrie *et al*⁵ and Trimble⁶ reported that several cases of psychoses emerged during add-on therapy with newer antiepileptic drugs such as vigabatrin, felbamate, lamotrigin, tiagabine, and topiramate. Because the mechanisms of action of these newer drugs vary, antiepileptic drug related psychoses may be indirectly rather than directly linked to their pharmacological action.

Changes in antiepileptic drug regimens, such as add-on therapy with a potent antiepileptic drug, abrupt discontinuation of existing antiepileptic drugs, or overdose, may all provoke psychoses. Suppression of epileptic activity in

the cortex with simultaneous preservation, or strengthening of seizure activity in deep brain regions may be the underlying mechanisms.^{7, 8} McKenna *et al*⁹ speculated that both episodic and chronic psychoses may be related to increased seizure activity in deep brain regions, and patients exhibiting both postictal and alternative psychoses¹⁰ support this hypothesis.

In the present study, changes in the antiepileptic drug regimen were not sufficient to treat the psychotic episodes, and all patients in the drug related group needed adjunctive psychotropic drugs. Among those who relapsed into psychoses, more than half of the incidences were in the absence of psychotropic maintenance therapy. These findings suggest that patients with a history of antiepileptic drug related psychoses are more vulnerable to the development of psychoses. Trimble¹¹ suggested that there is a disturbance of monoamine metabolism in these patients, and speculated that an increase in central dopamine activity caused by antiepileptic drug medication may increase their risk of developing psychoses. Based on these findings, those patients may require long term combined therapy with antiepileptic drugs and psychotropic drugs after a psychotic episode. Furthermore, we emphasise that changing antiepileptic drug regimens gradually and ensuring compliance with existing therapy are crucial factors in preventing psychoses in epileptic patients.

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