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Impact of antiepileptic drugs on genesis of psychosis

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ABSTRACT

Opinions regarding the impact of antiepileptic drugs (AEDs) on the genesis of psychotic symptoms are varied. To re-examine this issue, the records of adult patients with partial epilepsy and newly added AEDs were retrospectively surveyed. The types of newly added AEDs and clinical characteristics were compared between 38 patients with active psychosis and 212 without psychotic history during a follow-up period of 3 to 6 months after initiation of AED administration. Using multivariate logistic regression analysis, the significance of possible predictive variables for development of psychosis was evaluated, which demonstrated that use of zonisamide (ZNS) and phenytoin (PHT), presence of complex partial seizures (CPS), and low intelligence level were significantly correlated with psychosis. We concluded that ZNS and PHT are possible risk factors for development of psychosis along with clinical variables, including the presence of CPS and low intelligence level.

1. Introduction

The incidence of psychosis in patients with epilepsy is known to be higher than that in the healthy general population [1,2]. A national study conducted in Denmark reported that individuals with epilepsy had 2–3 times the risk of psychosis as compared with the general population [3]. This increased incidence has also been shown to be more marked in patients with temporal lobe epilepsy (TLE) [4–7].

Several factors are speculated to be mutually involved in the development of psychosis in patients with epilepsy, including intelligence, heredity, and other clinical features associated with seizures and electroencephalographic abnormalities [8–12]. However, the impact of antiepileptic drugs (AEDs) on the genesis of psychotic symptoms remains controversial. Some authors have insisted that psychotic symptoms in patients with epilepsy are caused by the use of specific AEDs [13–16], while others noted that even psychotic symptoms apparently induced by initiation of AEDs persisted or recurred in spite of discontinuation of the suspected drug in approximately 20% to 40% of patients [7,15]. Despite the importance of the question, few studies dedicated to the role of AEDs in occurrence of psychotic episodes in patients with epilepsy have been presented, except for a few notable exceptions. The unique situation in Japan, where new AEDs have become available while traditional drugs such as phenytoin and phenobarbital are still being actively used, is favorable to examine this situation.

In order to identify predictive variables in the development of psychosis, we retrospectively conducted a case–control study of adult patients with epilepsy. The key characteristics of our study were as follows: 1) Only adult patients with partial epilepsy were selected as subjects. 2) All patients were registered when any AED was newly added or any psychotic episode newly occurred. 3) The differential contributions of clinical characteristics and types of AED were analyzed with regard to psychotic episodes.

2. Methods

2.1. Selection of subjects

We enrolled adult patients (15–64 years old) with partial epilepsy who were treated for 3 months or more at our epilepsy care units, subunits of the Department of Psychiatry, Aichi Medical University, between April 1985 and January 2011. All patients met the criteria for epilepsy as set forth in the International Classification of Epilepsies. Patients who had premorbid psychosis antedating the development of epilepsy, evidence of senile dementia, substance abuse, or recent progressive mass lesions were excluded from the study. In addition, only patients with partial epilepsy initially confirmed to be in a state without active psychosis, and those who developed a psychotic episode after an AED was introduced were included. As a result, the records of 38 patients who exhibited a psychotic episode (index group) and those of 212 without any history of psychosis (control group) were extracted and analyzed. Patients were classified into the index group when any evidence of psychotic symptoms

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was confirmed during the follow-up period, which was an average 5.54 months, after initiation or addition of a new AED.

2.2. Definition of psychosis

Psychosis was defined as the presence of hallucinations, delusions, or a limited number of severe behavioral abnormalities in accordance with the ICD-10 criteria [17] for mental and behavioral disorders. In a state of full consciousness, such patients exhibited psychotic episodes lasting for more than 24 h.

2.3. Investigation items

The following items were investigated.

2.3.1. Clinical characteristics

1) Types of partial epilepsy classified into 4; TLE, frontal lobe epilepsy (FLE), occipital lobe epilepsy (OLE), and others including multifocal epilepsy and partial epilepsy with unknown localization (M/ULE). 2) Age at the time of survey. 3) Age at onset of epilepsy. 4) Level of intelligence classified into 3 types; normal, borderline intellectual functioning, and mild/moderate mental retardation, as defined by the ICD-10 criteria. 5) Presence or absence of febrile seizures. 6) Gender. 7) Family history of epilepsy and psychosis in first-degree relatives. 8) Laterality of abnormal EEG findings classified into 4 categories; left hemisphere, right hemisphere, bilateral hemispheres, and no findings. 9) Laterality of brain imaging findings classified into 4 categories; left hemisphere, right hemisphere, bilateral hemispheres, and no findings. 10) Presence of CPS. 11) Presence of both primary and secondary generalized tonic-clonic seizures (GTC).

2.3.2. Use of AEDs

Newly added AEDs included the following: phenobarbital (PB), phenytoin (PHT), carbamazepine (CBZ), zonisamide (ZNS), valproic acid (VPA), clobazam (CLB), topiramate (TPM), gabapentin (GBP), lamotrigine (LTG), and levetiracetam (LEV). Furthermore, the use of monotherapy or polytherapy was also included in the list of possible independent variables.

2.4. Analytical methods

To identify predictive variables associated with epileptic psychosis, we analyzed our results using the following processes:

1) The 11 clinical characteristic variables were compared between the index group (n = 38) and control (n = 212) patients using a χ^2 test, *t*-test, or Fisher's exact test. From those results, variables with a value of $P<0.2$ were selected. Next, the 10 AED use variables were analyzed using a χ^2 test to select those with a value of $P<0.2$. Then, univariate logistic regression analysis was performed to calculate the odds ratios of the selected AEDs, after which, variables with an odds ratio greater than 1 were extracted.
2) Multivariate logistic regression analysis was performed using the variables extracted in the first and second steps noted above to identify predictive variables adjusted for confounding factors among them and to examine the predictability of developing psychosis.

The statistical software package SPSS 19.0 was used to perform the analyses, and values of $P<0.05$ were considered to be significant [18].

3. Results

1) In 8 patients in the index group, psychotic episodes occurred within 7 days after a decisive seizure or seizure cluster. Of those, psychotic episodes occurred exclusively after a seizure or seizure cluster in 5 patients, while psychotic episodes also occurred during the interictal period in the remaining 3. In all index group patients, no definite episode of complete replacement of seizure with psychosis was confirmed.
2) Table 1 shows the clinical characteristics of the patients in the 2 groups and results of our comparisons. Selected variables with a value of $P<0.2$ in the comparisons were age at onset of epilepsy, intelligence level, presence of CPS, locus of EEG abnormalities, and use of monotherapy or polytherapy.
3) Table 2a shows use of AEDs in the 2 groups and results of our comparisons. Selected variables with a value of $P<0.2$ in the comparisons were 6 different AEDs; PB, PHT, ZNS, GBP, LTG, and LEV. Odds ratios with the selected AEDs are shown in Table 2b. Using univariate logistic regression analysis, 3 AEDs with an odds ratio greater than 1 were extracted as possible predictive variables; ZNS, PHT, and PB, while GBP, LTG and LEV were eliminated due to an odds ratio less than 1.
4) The results of multivariate logistic regression analysis using 8 variables, age at onset of epilepsy, intelligence level, presence of CPS, locus of EEG abnormalities, use of monotherapy or polytherapy, and use of ZNS, PHT and PB, were as follows: First, a correlation matrix of the 8 individual-extracted variables was produced in advance to confirm the absence of multicollinearity. Then, multivariate logistic regression analysis was performed using the likelihood ratio method, a forward selection method, with the results shown in Table 3. The results of a model χ^2 test were significant at $P<0.01$, and each factor was also found to be significant. Confidence intervals for the odds ratios did not include 1, indicating significance. Thus, the following 4 significant variables indicating the predictability of psychosis were found; 1) use of ZNS (OR, 5.109), 2) intelligence level (borderline; OR, 2.878/MR; OR, 3.089), 3) use of PHT (OR, 2.938), and 4) presence of CPS (OR, 2.631). According to a logistic regression model

Table 1
Clinical characteristics of all patients.

	Epilepsy with psychosis (38)	Epilepsy without psychosis (212)	Value	*P*
Sex (male/female)	23/15	139/73	0.359[a]	0.549
Mean age at evaluation in years (SD)	38.6 (7.9)	38.0 (13.1)	−0.287[b]	0.775
Mean age at onset of epilepsy in years (SD)	13.5 (10.5)	19.2 (13.9)	2.39[b]	0.017
Type of epilepsy *(TLE/FLE/OLE/M/ULE)*	28/3/0/7	127/20/10/55	3.59[a]	0.308
CPS (positive/negative)	30/8	132/80	3.93[a]	0.047
GTC (positive/negative)	25/13	129/83	0.333[a]	0.564
Febrile seizures *(Positive/negative)*	7/31	27/185	0.886[a]	0.346
Family history of epilepsy *(Positive/negative)*	3/35	17/195	0.001[a]	0.979
Family history of psychosis *(Positive/negative)*	1/37	2/210	0.775[a]	0.392
Intellectual function *(Normal/borderline/MR)*	18/10/10	156/32/24	10.92[a]	0.004
Locus of EEG abnormalities *(L/R/bilateral/no discharge)*	11/6/6/15	38/26/24/124	4.838[a]	0.184
Locus of MRI abnormalities *(L/R/bilateral/no finding)*	3/6/5/24	22/17/10/163	2.782[a]	0.249
Monotherapy or polytherapy	4/34	77/135	9.789[a]	0.002

GTC: generalized tonic-clonic seizures, CPS: complex partial seizures.
Border: borderline intellectual functioning, MR: mental retardation.
[a] χ^2 test/Fisher's exact test.
[b] *t*-test.