Impact of antiepileptic drugs on genesis of psychosis
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A B S T R A C T
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.

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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. 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), clonazepam (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 $x^2$ 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 $x^2$ 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 $x^2$ 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>
<thead>
<tr>
<th>Table 1 Clinical characteristics of all patients.</th>
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<tbody>
<tr>
<td></td>
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<tr>
<td>Epilepsy with psychosis (38)</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td>Sex (male/female)</td>
</tr>
<tr>
<td>Mean age at evaluation in years (SD)</td>
</tr>
<tr>
<td>Mean age at onset of epilepsy in years (SD)</td>
</tr>
<tr>
<td>Type of epilepsy (TLE/FLE/OLE/M/ULE)</td>
</tr>
<tr>
<td>CPS (positive/negative)</td>
</tr>
<tr>
<td>GTC (positive/negative)</td>
</tr>
<tr>
<td>Febrile seizures (Positive/negative)</td>
</tr>
<tr>
<td>Family history of epilepsy (Positive/negative)</td>
</tr>
<tr>
<td>Family history of psychosis (Positive/negative)</td>
</tr>
<tr>
<td>Intellectual function (Normal/borderline/MR)</td>
</tr>
<tr>
<td>Locus of EEG abnormalities (L/R/bilateral/no discharge)</td>
</tr>
<tr>
<td>Locus of MRI abnormalities (L/R/bilateral/no finding)</td>
</tr>
<tr>
<td>Monotherapy or polytherapy</td>
</tr>
</tbody>
</table>

Border: borderline intellectual functioning, MR: mental retardation.
* $x^2$ test/Fisher’s exact test.
* I-test.
Table 2a

<table>
<thead>
<tr>
<th>Antiepileptic drugs used by study subjects.</th>
<th>Epilepsy with psychoses</th>
<th>Epilepsy without psychoses</th>
<th>Value</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>PB</td>
<td>9</td>
<td>16</td>
<td>9.324</td>
<td>0.006</td>
</tr>
<tr>
<td>PHT</td>
<td>15</td>
<td>36</td>
<td>10.040</td>
<td>0.002</td>
</tr>
<tr>
<td>CBZ</td>
<td>25</td>
<td>135</td>
<td>0.093</td>
<td>0.761</td>
</tr>
<tr>
<td>VPA</td>
<td>10</td>
<td>48</td>
<td>0.244</td>
<td>0.677</td>
</tr>
<tr>
<td>ZNS</td>
<td>18</td>
<td>32</td>
<td>20.978</td>
<td>0.000</td>
</tr>
<tr>
<td>CBZ</td>
<td>8</td>
<td>56</td>
<td>0.417</td>
<td>0.485</td>
</tr>
<tr>
<td>GBP</td>
<td>1</td>
<td>23</td>
<td>2.507</td>
<td>0.141</td>
</tr>
<tr>
<td>TPM</td>
<td>7</td>
<td>49</td>
<td>0.408</td>
<td>0.523</td>
</tr>
<tr>
<td>LGT</td>
<td>1</td>
<td>31</td>
<td>3.937</td>
<td>0.047</td>
</tr>
<tr>
<td>LEV</td>
<td>0</td>
<td>27</td>
<td>5.426</td>
<td>0.019</td>
</tr>
</tbody>
</table>

Values were obtained using a $\chi^2$ test or Fisher’s exact test.

4. Discussion

We conducted a case-control study of 38 psychotic and 212 control adult patients with partial epilepsy to examine clinical background and use of AEDs related to the development of psychosis. Logistic regression analysis findings showed that 4 variables were statistically significant in predicting the probability of psychosis development: use of ZNS, low intelligence level, use of PHT, and presence of CPS.

Our findings indicate that intellectual disability is related to the development of psychosis. This agrees with the prevailing view that the prevalence of psychosis in individuals with mental retardation or borderline intellectual functioning is higher than that in those with normal intelligence [19–22]. Another variable shown to have predictive value was presence of CPS. Most previous authors, including Schmitz and Wolf [8], as well as Adachi et al. [11,22], agree that the presence of CPS is significantly associated with development of psychoses.

In our logistic regression analysis, the use of ZNS showed the highest odds ratio among the 4 significant variables for the development of psychosis. ZNS is a novel anticonvulsant given as adjunctive treatment in combination with other antiepileptic medications for partial seizures and has been used in Japan and Korea for over 15 years. A line of case studies [23–27] has reported occurrence of frank psychosis in patients who received ZNS. Matsuura and Trimble [27] reported that the incidence of psychosis in patients treated with ZNS ranged from 1.9% to 2.3%, while the study of Miyamoto et al. [28] of 74 patients found that the incidence was much greater, ranging from 13% to 18%. According to the studies of White et al. [29] and Weinstauber et al. [30], who used logistic regression analysis, ZNS possibly triggers various psychiatric symptoms, including depression, anxiety, and irritability, as well as psychosis. In a study by Okada et al. [31], ZNS use was associated with increased extracellular dopamine levels in the striatum and hippocampus of rats, and their findings are consistent with several studies in which ZNS was found to be effective for treatment of Parkinson’s disease [32]. Therefore, it is considered that the effect of ZNS on dopamine might be associated with development of psychosis, though it is unclear whether ZNS monotherapy causes mental side effects.

In the current study, PHT was also shown to be associated with the occurrence of psychosis. Indeed, according to McDanal et al. [33], PHT may provoke schizophrenia-like psychosis at serum levels above 35 mg/L. However, even after cautiously excluding such cases of PHT toxicity, psychotic reactions were found to occur in patients with epilepsy who are treated with PHT [7,33–36].

In the present study, TPM was not listed among the factors relevant to psychosis. However, simple ranking indicated that TPM use was associated with the highest frequency of psychotic episodes among the newer AEDs, except ZNS. This agrees with some previous studies [37,38] that pointed to TPM as a possible cause of psychotic reaction in patients with epilepsy and is an issue worth examining in further studies. Previous findings concerning LEV in regard to psychotic reactions are conflicting [39,40], and the size of our sample administered LEV should be augmented before drawing a definitive conclusion. Finally, in the current study, GBP and LTG tended to be inversely correlated with development of psychosis. This may agree with previous reports [30–39] and suggests beneficial effects of these drugs on mental functioning.

Psychotic episodes during monotherapy have rarely been reported [28]. In the study of Schmitz [34], AED polytherapy was significantly related to psychosis, which was seen in 80% of their patients in the psychotic group as compared to 46% of the controls. In our study, the rate of polytherapy in the index group was significantly higher than that in the control group, though polytherapy was not extracted as an independent variable contributing to the development of psychosis in the ensuing multivariate logistic regression analysis.

In conclusion, our data suggest that ZNS and PHT are possible risk factors for development of psychosis, along with clinical variables including presence of CPS and low intelligence level. While the latter variables are intrinsic to the disease and unavoidable, the former can be avoided in patients particularly susceptible to psychosis. Considering the detrimental impact of psychosis on quality of life, accumulation of knowledge about avoidable risk factors is important in further studies.

Table 2b

<table>
<thead>
<tr>
<th>AED</th>
<th>Wald OR 95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>PB</td>
<td>8.365 3.802 1.538–9.397</td>
<td>0.004</td>
</tr>
<tr>
<td>PHT</td>
<td>9.362 3.188 1.517–6.701</td>
<td>0.002</td>
</tr>
<tr>
<td>ZNS</td>
<td>18.477 5.062 2.417–10.605</td>
<td>0.000</td>
</tr>
<tr>
<td>GBP</td>
<td>2.105 0.222 0.029–1.696</td>
<td>0.147</td>
</tr>
<tr>
<td>LGT</td>
<td>3.067 0.164 0.022–1.240</td>
<td>0.080</td>
</tr>
<tr>
<td>LEV</td>
<td>0.000 0.000</td>
<td>0.998</td>
</tr>
</tbody>
</table>

OR: odds ratio, CI: confidence interval.

References

[34] Schmitz B. Psychiatric syndromes related to antiepileptic drugs. Epilepsia 1999;40(10):65–70.