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Seizure activity and individual vulnerability on first-episode interictal psychosis in epilepsy☆

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ABSTRACT

Objective: Despite a theoretical consensus that interictal psychosis (IIP) is related to various epilepsy-related factors, the impact of seizure activity on development of IIP remains inconclusive. This is the first controlled study using quantitative seizure-activity measures at the onset of IIP.
Methods: One hundred and eighty-one patients with epilepsy who exhibited first-episode IIP (IIP group) and 427 patients with epilepsy without psychotic episodes (control group) were enrolled. The control group was matched for age, epilepsy type, and duration of epilepsy. The two seizure-activity indices (seizure frequency at the time of onset of first-episode IIP and the number of seizures before the onset of IIP) were evaluated and compared between the IIP and control groups. Logistic regression analysis was used for extracting risk variables to develop first-episode IIP.
Results: The sum of previous seizures was greater in the IIP than in control groups. This was particularly the case in the patients with partial epilepsies (PE). Higher seizure frequency in the patients with PE was associated with the development of first-episode IIP while no association was found in the whole cohort or in the patients with generalized epilepsies (GE). Subsequent multivariate analysis revealed the sum of previous seizures and family history of psychosis as risk variables to first-episode IIP.
Conclusions: The accumulation of seizure-related damages and family history of psychosis is associated with the onset of IIP episodes, particularly in the patients with PE. Seizure activity and individual vulnerability to psychosis are likely to be interacted for as the development of IIP in patients with epilepsy.

1. Introduction

Interictal psychosis (IIP) in patients with epilepsy was defined as any psychosis developed under clear consciousness after the onset of epilepsy [1]. Interictal psychosis tends to occur on average 14–15 years after the onset of epilepsy [2,3]. There is a consensus that structural/functional alterations associated with epilepsy and treatment for seizures precipitate the development of IIP. Various epilepsy-related factors have been considered as precipitating factors for IIP, including type of epilepsy and seizures, laterality and locality of EEG abnormalities, and antiepileptic medication [1,4,5]. Seizure-activity measures, however, have been barely studied as for development of IIP [5]. There still exist two contradictory theories: frequent seizures precipitate genesis of IIP; IIP occurs when seizure frequency decreases. The former is hypothesized based on kindling effects during the seizure interval [6]. The latter is based on the epilepsy–psychosis antagonism theory as observed in cases of forced normalization and alternative psychosis [4].

Seizure activity can be assessed by two time-related measures: a snapshot measure and a longer-term measure. In terms of evaluating impact of seizure activity on development of IIP, seizure frequency shortly before the onset of first-episode IIP can be used as a snap-shot measure. Early studies [7,8] reported that patients with temporal lobe epilepsy (TLE) who suffered from long-lasting IIP, had lower frequency of seizures than patients with TLE without IIP. More recently, Mendez et al. [9] showed increased frequency of complex partial seizures (CPS) in patients with epilepsy with IIP compared with those without IIP, while other studies with smaller sample size demonstrated equivalent frequency of seizures between patients with epilepsy with IIP and those without [5]. In these studies, the seizure frequency was evaluated

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long after their first-episode IIP; therefore, possible effects of seizure activity on genesis of IIP could not be deducted as seizure frequency often changes in the course of epilepsy.

As a longer-term measure of seizure activity, the sum of seizures between the onset of epilepsy and that of IIP can be used to show accumulating effects of seizures on the genesis of IIP. Only a single study [2] examined the total number of seizures antedating the development of the index IIP episode, suggesting that patients with a higher number of previous seizures tended to develop IIP.

In addition, it is desired to compare seizure activity in people with first-episode IIP using predetermined seizure-activity measures with adequately matched control subjects. While there are numerous studies on first-episode functional psychoses [10,11], studies focussed on first-episode psychosis in epilepsy are rare.

In the current study, we retrospectively investigated two seizure-activity measures, i.e., seizure frequency at the onset of IIP and the total number of seizures, at the onset of IIP in patients with first-episode IIP and matched control patients without IIP.

2. Methods

2.1. Definitions of IIP

Psychosis was defined as the presence of hallucinations, delusions, or a limited number of severe behavioral abnormalities in accordance with the International Classification of Disease-10 (ICD-10) [12]. Interictal psychosis was defined as (a) occurrence of psychosis, (b) in clear consciousness, (c) without a decisive anteceding seizure or cluster of antecedent seizures, and (d) with the first psychotic episode having occurred after the development of epilepsy [1,13]. Cases with IIP that developed long after seizure remission were also included although these episodes were not literally interictal [14]. Patients with epilepsy with postictal psychosis (psychotic episodes occurring within 7 days after a decisive seizure or cluster of seizures) [15,16] and ictal psychotic phenomena [1] were excluded.

2.2. Subjects

We consecutively enrolled all the newly registered patients in the period between 1 January 1980 and 31 December 2010 in epilepsy outpatient clinics at the National Centre Hospital, Musashino Kokubunji Clinic or Adachi Mental Clinic on our multicenter epilepsy research database. We extracted the patients when (a) they developed their first-episode IIP during the follow-up period after the initial consultation; (b) they were examined immediately after the onset of their first-episode IIP; (c) their clinical characteristics before the onset of the first-episode IIP were recorded; and (d) they had no history of substance misuse or progressive brain disorders. A total of 181 patients met these criteria.

We selected 427 patients with epilepsy without any history of psychosis as a control group matched for age, sex, epilepsy type, and age at the onset of epilepsy. As in the IIP group, those with a history of substance misuse and progressive brain diseases were not included. Their other clinical characteristics, including seizure frequency, were masked at the time of the selection.

Our patients attended their clinics every two to twelve weeks in accordance with the national healthcare guidelines and were followed up for a mean of 15.4 years (standard deviation (SD) 10.6, range 1–49). Seizure frequency and psychosocial presentations of the patients had been recorded at each consultation. Treatment strategies for IIP [17] and clinical set-ups of our institutions [3] have been described in detail elsewhere.

2.3. Study items

Study data were recorded at the time of the examination. In the IIP group, it was immediately after the onset of the first-episode IIP. We obtained the following items for each patient in both groups: (a) sex; (b) age at the time of examination (thus onset of first-episode IIP); (c) age at onset of epilepsy; (d) the interval between onset of epilepsy and the time of examination; (e) a family history of psychotic disorders within first degree relatives [18]; (f) a family history of epilepsy in first degree relatives; (g) lateralization of abnormalities in routine scalp electroencephalogram (EEG) recordings, divided into four categories: left, right, bilateral, or none [19]; (h) presence of mesial temporal sclerosis (MTS) on brain magnetic resonance imaging (MRI) according to our routine qualitative analysis, categorized into the four groups: left, right, bilateral, or none [20]; (i) intellectual functioning, divided into normal (FIQ ≥ 85), borderline (85 > FIQ ≥ 70), and mentally disabled (70 > FIQ) in accordance with the DSM-IV [21]; (j) epilepsy type based on ictal clinical symptoms, EEG, and neuroimaging findings in accordance with the International Epilepsy Classification [22], divided into generalized epilepsies (GE) and partial epilepsies (PE); (k) aetiology of epilepsy; and (l) the number of antiepileptic drugs (AED) taken.

2.4. Seizure frequency and total number of seizures

We used two measures on seizure activity: (m) seizure frequency in each seizure type at the time of the examination; and (n) the total number of seizures prior to the time of the examination. The seizure frequency and total number of seizures were assessed using clinical notes, seizure diaries, and interviews with patients and their family members and/or carers. Types of seizures were divided into simple partial seizure (SPS), complex partial seizure (CPS), generalized tonic–clonic seizure (GTC) either primary or secondary, absence, myoclonic, and tonic seizures in accordance with the international seizure classification [23]. Frequency of each seizure type was evaluated into six categories: daily, weekly, monthly, yearly, less than yearly, and seizure-free for 3 years or more [19]. Seizure frequency was reviewed for approximately 1 year prior to the time of the examination. In the case of considerable variations of frequency during the observation period, that of the nearest period to the time of the examination was used as their recent seizure frequency measure. When patients had seizures less frequently than monthly, their seizure frequency was reviewed for a maximum of 3 years prior to the time of the evaluation. The total number of seizures was calculated as the sum of all the seizures antedating the time of the evaluation and classified into four categories: rare (2–10 times), mild (11–100 times), moderate (101–500 times), and severe (more than 500 times). In the case that the seizure frequency and the sum of seizures fell between two categories, it was operatively assigned to the higher category.

2.5. Reliability of psychiatric examinations

Six consultant neuropsychiatrists specializing in epileptology conducted the psychiatric examinations. We performed a reliability analysis with intraclass correlation coefficient (ICC) for psychiatric examinations among the neuropsychiatrists using the brief psychiatric rating scale [24] on two detailed case vignettes. The evaluation scores were highly reliable among the six clinicians (ICC = 0.964, 95% confidence interval (CI) 0.943–0.980, $F(35,135) = 28.1$, $p = 0.000$).

2.6. Statistical analysis

Differences in linear variables by categorical variables were subjected to analysis of variance (ANOVA). Correlation between categorical variables was examined with chi-square test or Fisher exact test. Correlations between rank-order variables were examined with Spearman's rank-order correlation coefficient. Subsequently, only the variables demonstrating a significant effect on the development of first-episode IIP in single-variate testing were fed into logistic regression analysis with backward stepwise elimination. To avoid multiple testing, Bonferroni correction method was used if necessary. p values of <0.05 were considered significant. All statistical analyses were performed

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