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Socio-economic impact on epilepsy outside of the nation-wide COVID-19 pandemic area

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Abstract

Objective: To identify people with epilepsy (PWE) who required extensive care before the novel coronavirus disease 2019 (COVID-19) pandemic that had world-wide impacts on medical care and on socio-economic conditions.

Methods: Consecutive PWE who were treated at the epilepsy center of Hiroshima University Hospital, which was located in the COVID-19 non-pandemic area, between March 2019 and August 2020 were enrolled. We evaluated clinical and socioeconomic factors that were associated with seizure exacerbation (an increase in seizure frequency) during the first 6 months after the COVID-19 pandemic started compared with the previous 6 months.

Results: Among the 196 PWE who were evaluated (mean age was 37.8 ± 16.2 years), there were 33 PWE (16.8%) whose seizure frequency had increased after the pandemic began. People with epilepsy with a seizure increase showed a significant association with living alone (p < 0.001), a higher seizure frequency (p < 0.001), negative findings on MRI (p = 0.020), history of dissociative seizure (p < 0.001), mood disorders (p < 0.001), insomnia (p < 0.001), and high psychological stress levels (p = 0.024) at baseline compared with PWE without seizure exacerbation. Multivariate logistic regression analysis revealed that “living alone” (odds ratio (OR) 3.69; 95%CI 1.29–10.52), “high seizure frequency at baseline” (OR 4.53; 95%CI 1.63–12.57), and “comorbidity of insomnia” (OR 9.55; 95%CI 3.71–24.55) were independently associated with seizure exacerbation.

Conclusions: Even in the non-pandemic area, PWE had seizure exacerbation, suggesting that clinicians should screen patients’ mental health before the outbreak to provide care, reduce the burden, and prevent social isolation in PWE. This should be addressed particularly in patients with medically refractory seizures with insomnia who live alone.

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1. Introduction

The seriousness of the rapidly spreading novel coronavirus disease 2019 (COVID-19) has had a tremendous impact on world-wide medical care [1]. This novel impact is also threatening people with epilepsy (PWE), with the spread of COVID-19 reportedly leading to exacerbation of epileptic seizures [2]. Novel coronavirus disease 2019 pandemic has both a direct pandemic impact (infection-related illness) and an indirect infodemic impact (socio-economic and psychological stress) on people [3]. Outcomes for PWE due to these impacts have been recently investigated in areas that are directly affected by the pandemic [4,5]. However, little evidence is available on this issue for areas that are not affected by the pandemic or in affected areas before the pandemic began. The media has spread information rapidly to non-pandemic areas before the infection began in the area, causing an invisible fear due to the proliferation of information [6,7]; thus, this situation...
should be addressed in such areas. Additionally, PWE is sensitive to a dramatic change in the social situation [8]. Therefore, this study aimed to clarify the features of PWE in the non-COVID-19-pandemic areas who were vulnerable to increased seizures when the nation-wide pandemic started in Japan. We hypothesized that PWE who are highly sensitive to socio-economic changes will be identified, and their data can be used to develop a strategy for PWE in future social change situations. Within the COVID-19 era, the major challenge will be to determine PWE who should receive flexible medical care or self-management in accordance with dynamic socio-economic changes that result from the threat of an emergent infectious disease [9].

2. Methods

2.1. Standard protocol approvals, registrations, and patient consent

This study was conducted at an epilepsy center in the division of neurology at Hiroshima University Hospital in Hiroshima prefecture, which has a population of 2.8 million people. There were only 458 people infected with COVID-19 in this prefecture at the end of August 2020 [10]. Thus, it could be defined as a “non-pandemic area” for COVID-19 in Japan. The total number of COVID-19 cases was 20,814 in Tokyo metropolitan area, the largest epidemic area in Japan, at the time. Meanwhile, 238,938 cases were reported in New York state [11].

We evaluated consecutive PWE who attended the epilepsy center whose medical history including their seizure type and seizure frequency data were available for the following two observational periods: a 6-month “pre-pandemic period” (between March 2019 and August 2019) and a 6-month “pandemic period” (between March and August 2020, which was a 6-month period after the pandemic started in Japan) (Fig. 1). These periods were determined based on the pandemic trend in Japan; the first pandemic wave emerged in March 2020 followed by the second wave that started in July 2020. There were 68,494 people who were infected with COVID-19 at the end of August 2020 in Japan [12]. To clarify the impact of the pandemic on the change in seizure frequency following the onset of the pandemic, we included only PWE who exhibited no increase in seizure frequency before the pandemic started, i.e., we excluded PWE with ≥50% increase in seizure frequency during the pre-pandemic period compared with a 6-month period before that (“reference period”, Fig. 1). Patients were also excluded if they had a history of unstable psychosis or alcoholism, or if they underwent an epilepsy surgery during the study periods. Given the accuracy of the seizure frequency that was reported, patients with dementia and learning difficulties were also excluded; however, if the seizure frequency data were precisely available from the caregiver, those patients were included. This retrospective study was approved by the Ethics Committee at Hiroshima University Hospital (No. E-2285), and all of the patients provided informed consent to participate.

2.2. Clinical parameters

Clinical data associated with epilepsy (seizure type, epilepsy classification, seizure frequency, and medication) were reviewed. We determined the seizure frequency during the pre-pandemic and pandemic periods, and then calculated the difference in seizure frequency between these periods to assess the increase in frequency after the pandemic started, i.e., the seizure exacerbation. Magnetic resonance imaging (MRI; structural abnormality) and electroencephalography (EEG; background activity, focal slow, and epileptic discharges) findings were investigated as the baseline status for each patient. In accordance with recent International League Against Epilepsy (ILAE) classification [13,14], epilepsy comorbidities and etiology were also assessed.

2.3. Socio-economic status

We reviewed data on the patients’ life history including occupation, income, and living situation (e.g., if the PWE lived alone, with their parents in a two-generation household, or with their parents and grandparents in a multi-generation household). To clarify the socio-economic changes during the study periods, we assessed the change in income by comparing the income level in the pre-
pandemic and pandemic periods. This income change was classified into five categories, which were “increase by $>$10%”, “neutral”, “decrease by $<$10%”, “decrease by 10–50%”, and “decrease by $>$50%”. A change in work style such as using telecommuting was also reviewed. Additionally, we investigated lifestyle changes in whether PWE had to take care of their children due to social changes (e.g., closing schools and declaring the emergency) after the pandemic began.

2.4. Psychological distress changes

Mood disturbances could be confounders of changes in seizure frequency because a seizure can be provoked due to a change to a negative mood. Thus, the short screening scale, six-item Kessler Psychological Distress Scale (K-6) [15,16], which was validated during the two study periods was reviewed to evaluate the changes in psychological distress during the pandemic. This scale measured how frequently the patients exhibited symptoms of psychological distress (e.g., feeling of depression, anxiety, and sadness) via a questionnaire in which the patients could rate their condition using a five-point scale for each of the six items. We assessed whether the K-6 total score changed during the two study periods. Data were not obtained from patients with severe learning difficulties and dementia even if seizure frequency were available from their caregiver.

2.5. Data analysis

The available clinical data from the pre-pandemic period was initially compared to the data from the pandemic period. The primary measure was a change in the habitual seizure frequency during the two periods, which was classified into the following three categories: amelioration ($\geq 50\%$ seizure reduction); neutral; or exacerbation ($\geq 50\%$ seizure increase). Unprovoked habitual seizure data were used for this calculation, while provoked seizure data, such as an antiepileptic drug (AED) withdrawal seizure and acute symptomatic seizure, were not included in this assessment. If a patient had multiple types of seizures (e.g., focal awareness seizure (FAS), focal impaired awareness seizure (FIAS), and focal to bilateral tonic–clonic seizure (FBTCS)), the most harmful and frequent seizure type was used for this seizure frequency calculation. Socio-economic factor changes were also assessed between the study periods.

Next, we examined the differences in clinical and socio-economic factors between patients with seizure exacerbation (exacerbation group; $\geq 50\%$ increase in seizure frequency during the pandemic period compared with the pre-pandemic period) and those without seizure exacerbation (non-exacerbation group; this is the sum of the “amelioration” and “neutral” groups). The statistical significance for the intergroup differences was determined using a Pearson’s chi-squared test for categorical variables, while an unpaired Student’s $t$-test or Welch’s $t$-test, depending on the variance was used for the continuous variables. Finally, clinical and socio-economic factors that were found to be significant ($p < 0.05$) in the univariate analysis were selected for subsequent logistic regression analysis using the forward stepwise method. We used the likelihood ratio test to calculate odds ratios (ORs). All statistical analyses were conducted using JMP software (JMP Pro version 14; SAS Institute, Cary, NC, USA). Values of $p < 0.05$ were considered to be significant.

3. Results

3.1. Patients’ characteristics

One hundred ninety-six consecutive PWE were included; 109 were men (55.6%) and the participants’ mean age was 37.8 ± 16.2 years (range, 16–82 years; Table 1). The most common epilepsy classification was focal epilepsy, among which the highest was temporal lobe epilepsy (27.1%) followed by frontal lobe epilepsy (18.4%). Over half of the patients had a history of bilateral tonic–clonic seizure (BTCS). Baseline habitual seizure frequency was variable. While the mean number of current AED use was 1.9 ± 1.3, the number of PWE who used only conventional AEDs, e.g., valproate acid or phenobarbital only, was 16.3%. Occupation status is also shown in Table 1.

3.2. Changes in seizure frequency and socio-economic status

Table 2 shows seizure outcomes and socio-economic factors after the pandemic onset. There were no PWE who were infected with COVID-19 or had close contact with a COVID-19-infected person. Over 60% of PWE remained “neutral” in their seizure frequency during the pandemic period compared to the pre-pandemic period. Meanwhile, 32 PWE (16.3%) showed “exacerbation” and 30 PWE (15.3%) showed “amelioration”. PWE with amelioration reported the following possible factors that were related to amelioration: (1) adjunct AED therapy reduced seizures; (2) going online reduced the stress of commuting or interpersonal stress; or (3) “stay-at-home” made it possible to secure sleep time. There were 18 PWE (9.2%) whose income decreased by 10% com-

| Table 1 Clinical characteristics of patients with epilepsy. |
|-------------------------------------------------------------|
| Patients with epilepsy (n = 196)                             |
| Age, years (mean ± SD)                                       |
| 37.8 ± 16.2                                                 |
| Onset age, years (mean ± SD)                                |
| 25.4 ± 17.5                                                 |
| Gender, male (n, %)                                         |
| 109, 55.6                                                   |
| Epilepsy classification (n, %)                              |
| Generalized epilepsy (n)                                    |
| 67, 34.2                                                    |
| Focal epilepsy (n)                                          |
| 99, 50.5                                                    |
| Temporal lobe epilepsy (n)                                  |
| 53, 27.1                                                    |
| Frontal lobe epilepsy (n)                                   |
| 36, 18.4                                                    |
| Unclassified (n)                                            |
| 30, 15.3                                                    |
| Seizure type (n, %)                                         |
| FAS (n)                                                     |
| 52, 26.5                                                    |
| FIAS (n)                                                    |
| 69, 35.2                                                    |
| Myoclonus (n)                                               |
| 22, 11.2                                                    |
| Focal to bilateral tonic–clonic seizure (n)                 |
| 62, 31.6                                                    |
| Bilateral tonic–clonic seizure (n)                          |
| 72, 36.9                                                    |
| Dissociative seizure (n)                                    |
| 30, 15.3                                                    |
| Seizure frequency (n, %)                                    |
| weekly or more (n)                                         |
| 26, 13.2                                                    |
| monthly (n)                                                 |
| 71, 36.2                                                    |
| yearly or less (n)                                          |
| 99, 49.5                                                    |
| Number of AEDs (mean ± SD)                                  |
| 1.9 ± 1.3                                                   |
| Drug-resistant epilepsy (n, %)                              |
| 37, 19.0                                                    |
| Only used conventional AEDs (n, %)                          |
| 32, 16.3                                                    |
| Occupation (n, %)                                           |
| Blue-collar worker (n)                                      |
| 15, 8.4                                                     |
| Office worker (n)                                           |
| 26, 14.6                                                    |
| Service industry (n)                                        |
| 19, 10.7                                                    |
| Medical staff (n)                                           |
| 9, 5.0                                                      |
| Self employed (n)                                           |
| 2, 1.1                                                      |
| Housewife (n)                                               |
| 16, 9.0                                                     |
| Student (n)                                                 |
| 29, 16.3                                                    |
| Unemployed (n)                                              |
| 62, 34.8                                                    |

AED, antiepileptic drug; FAS, focal awareness seizure; FIAS, focal impaired awareness seizure; BTCS, generalized tonic–clonic seizure; SD, standard deviation
*Data were available for 178 patients with epilepsy.
Differences in clinical characteristics between patients with or without seizure exacerbation following the pandemic

There were no significant differences observed for the current age, onset age, gender, AED treatment. Epileptic seizure types (FIAS, myoclonic seizure, or BTCS) were also not significantly different between the groups (Table 3). However, there were significantly more PWE who had a dissociative seizure in the exacerbation group than in the non-exacerbation group (46.9% vs. 9.2%, \( p < 0.001 \)). Habitual seizure frequency during the pre-pandemic period was also higher in the exacerbation group than in the non-exacerbation group (\( p < 0.001 \)). Prominent comorbidities in PWE in the exacerbation group included mood disorders (\( p < 0.001 \)) and insomnia (\( p < 0.001 \)). Electroencephalography findings showed no differences. In contrast, the only factor that was less evident in the exacerbation compared to the non-exacerbation group was structural abnormalities that were observed on MRI evaluation (\( p = 0.021 \)).

The mean K-6 score during the pre-pandemic period was significantly lower in the exacerbation group compared to the non-exacerbation group (22.9 ± 5.5 vs. 25.7 ± 6.0, \( p = 0.038 \)). This trend was also present in the pandemic compared to the pre-pandemic time (19.6 ± 6.1 vs. 25.5 ± 5.4, \( p < 0.001 \)).

### 3.4. Differences in socio-economic factors in association with seizure exacerbation following the pandemic

There were no significant differences in PWE’s income and the number of PWE who telecommuted or were required for childcare due to a social change (Table 4). A patient’s living situation was the only social factor that clearly distinguished between PWE with and without exacerbation, i.e., the number of PWE who lived alone was significantly higher in the exacerbation group compared with the non-exacerbation group (40.6% vs.12.8%, \( p < 0.001 \)). In contrast, the two-generation household status was strongly associated with non-exacerbation compared to the exacerbation group (31.3% vs. 60.3%, \( p < 0.001 \)).

### 3.5. Multivariate analysis

Multivariate logistic regression analysis revealed that “living alone” (odds ratio (OR) 3.69; 95%CI 1.29–10.52), “high seizure frequency at baseline” (OR 4.53; 95%CI 1.63–12.57), and “comorbidity of insomnia” (OR 9.55; 95%CI 3.71–24.55) were independently associated with seizure exacerbation (Table 5).

### 4. Discussion

The present study evaluated the change in seizure frequency and socio-economic conditions for PWE in a COVID-19 non-pandemic area to clarify the infodemic impact on PWE when the nation-wide pandemic started. While no PWE had exposure his-
A seizure recurrence generally relied on multiple underlying factors in PWE, sleep deprivation and psychological stress were the major causative factors [25–27]. A recent study showed that PWE with a history of mood disorders before the pandemic showed a significant association with an increase in seizure frequency during the pandemic [28]. Because mood disorders, such as anxiety and depressive disorders, are a main and common comorbidity in PWE [29], management of mental health for PWE is especially important in the current COVID-19 pandemic [20]. The COVID-19 pandemic directly threatens PWE in China [2], and an increased severe psychological stress in PWE has been observed [4]. A previous study claimed that psychological stress was associated with an increased risk in seizure recurrence [27]. Psychological stress severity was not different among PWE with variable seizure frequencies, which suggests that the degree of psychological stress that occurred during the COVID-19 pandemic was the same regardless of the seizure frequency [4]. For the change in seizure frequency during the pandemic, another observational study from Saudi Arabia showed that the baseline seizure frequency, more AEDs, noncompliance, self-rating stress, and change in sleep conditions were significant factors that were associated with seizure exacerbation during the pandemic [30]. Among those factors, seizure frequency and insomnia were also significant in the present study. This evidence suggests that a change in sleep conditions was a major contributor to seizure exacerbation even in non-pandemic areas. This risk might be especially true for PWE who have a high seizure frequency given our results. Because epilepsy-related mortality is higher in patients with refractory seizures than in those with well-controlled seizures [31], this risk could be critical. It is possible that such a situation (negative affect caused by the quality of sleep) was attributed to the COVID-19 infodemic [32]. Our results indicate that the participants who had a history of mood disorders and dissociative seizure and a low K-6 score (high psychological stress level) during the pre-pandemic period were significantly associated with seizure exacerbation. Thus, infodemic impact was probably greater in PWE with a history of mood disorders or dissociative seizure than in PWE without these conditions. Therefore, mental health, including abnormalities in the patient's psychiatric status, cognition, and social-adaptive behaviors, should be managed appropriately [33], especially for PWE who have risk factors that were identified in the present study. Meanwhile, multiple PWE (15.3%) notably showed decrease in seizure frequency during the pandemic period due to their social background change. This result suggested that some PWE felt comfortable in the “new normal” COVID-19 era.

PWE with seizure exacerbation likely lacked structural abnormalities on MRI in the present study. This could be reasonable because the MRI negative focal epilepsy involved patients with medically refractory focal epilepsy [34]. Thus, negative MRI results could be confounders between the high seizure frequency during the pre-pandemic period and seizure exacerbation during the pandemic period.

Several limitations were associated with the present study. First, the study was limited by its retrospective design. Although it was a single-center evaluation, our hospital is the largest epilepsy center in the prefecture that followed multiple kinds of PWE. Conversely, the participants could be characterized as having a good education about self-management relative to PWE in a local hospital that did not specialize in epilepsy. This inequality was not addressed in the present study. Second, the seizure frequency that was observed during the study periods was not objectively evaluated. The accuracy of the self-reported seizure frequency in PWE could be less reproducible [35]. Third, the internet and social media can be a source of uncertain or misleading information that can lead people to react incorrectly or behave with anxiety [36]. Although the impact of the infodemic greatly relied on how much these sources were used, our multivariable analysis did not include

| Table 5 | Multivariate analysis of factors associated with seizure exacerbation. |
|---------|-----------------------------|
|          | OR  | 95%CI       | P value |
| No housemate | 3.69 | 1.29–10.52 | 0.015 |
| Seizure frequency, monthly or more | 4.53 | 1.63–12.57 | 0.004 |
| Comorbidity of insomnia | 9.55 | 3.71–24.55 | <0.001 |

We performed multivariate analyses using the following factors: dissociative seizure, seizure frequency, MRI abnormality, comorbidity of mood disturbance and insomnia, and K-6 score (baseline). OR, odds ratio; CI, confidence interval.
such confounders, i.e., PWE who are ignorant of information from the media. Because self-management education in PWE is known to reduce their seizure frequency and seizure-induced adverse events [37], the negative impact of an infodemic should be explored in a future study. Finally, several social factors remain, i.e., the patient’s personal social network, frequency of hospital visits, use of social network services, and effect of restricting action by declared state of emergency were not investigated in the present study.

5. Conclusion

Even in the non-pandemic area, our study confirmed that seizure exacerbation can be present before the pandemic start, and identified the features of PWE who have a high risk of the exacerbation during a pandemic and other public health emergencies. Clinicians should keep in touch with these PWE and pay more attention to their social isolation during non-pandemic times. Screening for psychiatric and behavioral health disorders that were measured before the outbreak would address the need for therapy to reduce the burden and seizure frequency and improve the patients’ quality of life.

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Declarations of interest

None.

Data availability statement

The data of this study will be available from the corresponding author upon reasonable request.

Authorship

- Shuichiro Neshige; design and conceptualized study; analyzed the data; drafted the manuscript for intellectual content.
- Hirofumi Maruyama; conceptualized study; interpreted the data.
- Takeo Shishido; conceptualized study; interpreted the data.
- Hiroki Morino; revised the manuscript for intellectual content.
- Hiroyuki Morino; interpreted the data; revised the manuscript for intellectual content.
- Shiro Aoki; conceptualized study; analyzed the data.
- Koji Iida; conceptualized study; interpreted the data.
- Hiroyuki Morino; revised the manuscript for intellectual content.

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