Treatment strategies of status epilepticus in the elderly: a report from a single center in Japan

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Abstract

Purpose: To investigate treatment strategies for status epilepticus (SE) in elderly patients.
Methods: The medical records of all patients aged ≥ 60 years who were admitted to Aizawa Hospital in Matsumoto because of ‘epilepsy’ or ‘seizure’ between April 2012 and January 2015 were retrospectively reviewed. We found 54 patients, and 11 of them had status epilepticus. We investigated their age, sex, causes, seizure types, responses to medication and outcome.
Results: The ages of the patients with SE were significantly higher than the ages of those without SE (p = 0.02). The cause of seizures was cerebrovascular diseases in 50% of the patients. Six patients with SE were administered diazepam suppository (4-8 mg) three to four times daily combined with intravascular phenytoin. No patient needed a ventilator during the period of SE or died from SE. The number of SE patients who did not recover the ability of oral intake after recovery from SE was significantly higher in those with secondary generalized seizures (p = 0.04) than in those with complex partial seizures. The patients who did not recover the ability of oral intake had significantly longer SE compared to those who recovered oral intake (p = 0.005).
Conclusion: A treatment strategy that is potent enough to abort seizures and at the same time has less serious adverse effects is desirable for elderly patients with SE.
Introduction

The number of elderly people who develop epileptic seizures has been increasing in many countries along with an overall increase in the elderly population [1, 2]. The causes of epileptic seizures have age-related characteristics, and treatment is more challenging for elderly patients compared with younger patients. Status epilepticus in the elderly, in particular, is a critical factor that degrades the level of activities of daily living and increases mortality [3]. Emergency medical treatment for status epilepticus tends to have serious negative effects on the vital condition in the elderly, and a long period of severe, sustained post-epileptic morbidity is not uncommon.

Analyses of clinical symptoms, etiologies and outcome of treatment are necessary to identify appropriate treatment strategies for epileptic seizures in the elderly. We reviewed the charts of elderly patients who were admitted with epileptic seizures to Aizawa Hospital in Matsumoto, Japan. We analyzed the course of treatment, especially focusing on status epilepticus (SE).

Methods

Aizawa Hospital is in the central region of Matsumoto, a city located in the middle of the Japanese mainland with a population of approximately 240,000 in 2015. Aizawa Hospital has a capacity of 502 beds and an Emergency Medical Center, and has been accepting approximately 7000 emergency transports per year. The hospital database was retrospectively searched to identify all patients ≥ 60 years who were admitted because of 'epilepsy' or 'seizure' between April 2012 and January 2015. Medical records, brain images and laboratory data were reviewed. We found 54 patients, and 11 patients among them showed SE. SE was diagnosed according to the following definition: seizures that persist for longer than 30 minutes or recurrent epileptic activity over a period of longer than 30 minutes [4, 5]. Non-convulsive status epilepticus (NCSE) was diagnosed according to the following definition: a range of conditions in which electrographic seizure activity is prolonged for longer 30 minutes and results in non-convulsive clinical symptoms [6]. Acute symptomatic seizure was diagnosed following the definition recommended by the International League Against Epilepsy [7].

We investigated the age, sex, causes, seizure types, neuroradiological findings, functional condition, and responses to medication. Functional condition was determined by assessing the ability of oral intake before seizure onset and after termination of seizures. The causes were categorized following the classification recommended by ILAE [8].

With regards to the treatment of seizures in elderly patients, intravenous injection (IV) of diazepam (DZP) was routinely used to terminate convulsion followed by IV phenytoin (PHT) twice daily in the subsequent period. In the case of SE, diazepam suppository (DZP supp) was frequently used instead of IV infusion of midazolam (MDZ) as long as the patient's vital capacity was stable, in order to avoid respiratory depression.

The statistics package, SYSTAT13 was used for analyses. The Yates' corrected chi-squared test was used for comparison of the number of patient groups with different outcomes. The Mann-Whitney test was used for comparison of the ages in the SE group and
the non-SE group, along with the durations of SE in the patient groups with different outcomes. Differences were considered significant when \( p \) was < 0.05 (two-sided).

This study was approved by the ethics committee of Aizawa Hospital for research on human subjects and conducted according to the Helsinki declaration.

**Results**

*Age distribution*

Figure 1 shows the distribution of all patients with seizures (\( n = 54 \)) and patients with SE (\( n = 11 \)) by age. For all patients with seizures, the number of female patients was greater than that of male patients (32:22). The mean age of all patients was 79.5 years; 80.8 years in females and 77.6 years in males. The age distribution showed that the proportion of patients with seizures was higher in the 70's and 80's than in the 60's and 90's. Considering that the population decreases with increasing age, the present data suggested that the incidence of seizures is higher in the 70's and 80's than in the 60's.

Eleven patients (20% of all patients) showed evolution to SE. This group comprised 8 females and 3 males. The mean age of patients with SE was 86.5 ± 10.2 years (mean ± standard deviation), and was significantly higher (\( p = 0.02 \)) than the mean age of those without SE (77.7 ± 9.0 years). The age distribution of the patients with SE clearly showed an increase in prevalence in the older age group (Table 1).

**Table 1. Summary of the cases with SE.**

| Onset age/sex | Causes          | Seizure types | Medication                        | SE duration | Ability of oral intake before → after |
|---------------|----------------|---------------|-----------------------------------|-------------|---------------------------------------|
| 69/F          | neurofibromatosis | CPS           | IV PHT, DZP supp                  | 32 hours    | +                                     |
| 72/M          | stroke           | CPS           | IV PHT, DZP supp                  | 5 hours     | +                                     |
| 80/F          | stroke           | SGS           | IV DZP, IV PHT                    | 2 hours     | +                                     |
| 84/F          | stroke           | SGS           | IV PHT, IM PB, DZP supp           | 3 hours     | +                                     |
| 84/F          | brain tumor      | SGS           | IV DZP, IV PHT, IM PB, DZP supp   | 24 hours    | -                                     |
| 87/F          | stroke           | SGS           | IV PHT, DZP supp                  | 24 hours    | +                                     |
| 88/M          | stroke           | CPS           | IV PHT                            | 24 hours    | +                                     |
| 91/F          | encephalitis     | SGS           | IV DZP, IV PHT, DZP supp          | 7 days      | +                                     |
| 96/F          | Alzheimers       | CPS           | correction of Na                  | 1 hour      | +                                     |
| 100/F         | Alzheimers       | SGS           | IV PHT                            | 3 days      | +                                     |
| 100/M         | Alzheimers       | CPS           | Antibiotics                       | 24 hours    | +                                     |

SE: status epilepticus, CPS: complex partial seizure, SGS: secondary generalized seizure, IV: intravenous injection, PHT: phentoin, DZP: diazepam, DZP supp: diazepam suppository, IM: intramuscular injection, PB: phenobarbital
Etiologies and types of seizures

Figure 2 shows the etiologies of seizures. All patients had some diseases that were estimated to cause the seizures. The causes of seizures in all patients were cerebrovascular diseases in 50%, degenerative brain diseases in 15%, neoplasms of the brain in 11%, metabolic brain diseases in 7%, and miscellaneous in the remaining cases. The causes of seizures in the patients with SE (Table 1) were cerebrovascular diseases in 45%, degenerative brain diseases including multiple causes in 27%, and neoplasms of the brain in 9%, showing the same order of frequency as in all patients with seizures.

Of all patients, 76% manifested partial seizures evolving to secondary generalized seizures (SGS), and 22% had complex partial seizures (CPS). Of the 11 patients with SE, 6 showed SGS, 5 manifested CPS, and one patient with CPS had NCSE.

Treatment of SE

Treatment of SE is summarized in Table 1. Following the acute stage, 9 of the 11 patients with SE were treated with IV PHT (125-250 mg) twice daily, and 6 patients were treated with DZP supp (4-8 mg) three to four times daily in combination with IV PHT. In 2 patients with acute symptomatic seizures showing CPS, only treatment for the underlying causes was given. The periods of SE ranged from 1 hour to 7 days (mean 43 hours). No patient needed a ventilator or tracheal intubation during the period of SE, and no patients died from SE. Most patients showed somnolence during SE, but it was unclear whether such change was derived from DZP supp or from the seizure itself. The number of SE patients who did not recover the ability of oral intake after recovery from SE was significantly higher in those manifesting SGS (5 of 6, p = 0.04) than in those with CPS (1 of 5) (Fig. 3A). The patients who did not recover the ability of oral intake had significantly longer SE than those who recovered oral intake (p = 0.005) (Fig. 3B). The patients who had not recovered oral intake started tube feeding or intravenous rehydration.

Figure 2. Etiologies of seizures in all patients with seizures (n = 54).

Figure 3. A: Number of patients with status epilepticus (SE) manifesting complex partial seizures (CPS) or secondary generalized seizures (SGS) who did and did not recover the ability of oral intake after recovery from SE. B. The duration of SE in patients who did and did not recover the ability of oral intake.
Discussion

We found female preponderance (female/male = 1.45) in our patients with seizures aged 60 years and older. According to the demographics of Japan in 2015, the female/male ratio for the population aged ≥ years was 1.25 [9]. Consequently, there was a clear female preponderance in patients with seizures in the series. A slight female preponderance was also reported in US Medicare beneficiaries [10]. The age distribution of our patients showed a larger proportion of patients in their 70's and 80's compared to those in their 60's. This tendency is consistent with the U-shape distribution of the incidence of epilepsy reported in a large population study [1]. The ages of patients with SE were distributed in the higher age group among all elderly patients with seizures in the present study. It has been suggested that drug use is a risk factor of SE, in addition to stroke and degenerative diseases [11].

The analysis of etiologies of seizures in all patients with seizures showed that the major cause was cerebrovascular diseases (one-half of all cases), followed by neurodegenerative diseases, brain tumors, and metabolic disorders in the present study. These results are in agreement with those from previous studies showing acute stroke as the most common cause of new-onset epilepsy, accounting for up to one-half of the cases [2, 12]. As to the type of seizures, all our patients had partial seizures, 76% of whom were associated with secondary generalization and 24% were CPS. Previous studies disclosed that most new seizures in elderly patients were partial at onset [12, 13]. Twenty percent of our patients had SE, and previous report showed that approximately 30% of new-onset seizures in the elderly had SE [14]. SE tended to occur in patients with older age in the present study. The etiologies and seizure types of our patients with SE showed a similar tendency as those of all patients with seizures.

With regard to treatment for seizures, elderly people with epilepsy generally respond well to anti-epileptic drugs (AEDs). Therefore, initiation of AEDs after onset is generally recommended. On the other hand, a guideline of emergency treatment of seizures, especially SE, in elderly patients has not yet been established [15]. The principle of treatment for SE, in general, is prompt termination of seizures in order to avoid cerebral damage, and intensive care using assisted ventilation is common. The International League Against Epilepsy (ILAE) proposed early initiation of treatment of SE within 5 minutes of onset for generalized convulsive SE [16]. The present study and previous research have shown that the most frequent types of SE in the elderly are focal SE and non-convulsive SE [17], and these types present less severe cardiorespiratory depression than does generalized convulsive SE. This tendency may suggest the possibility that SE in elderly patients produces less damage to the brain. The results from the present study, however, showed that the severity of convulsion and the duration of SE lead to poor outcome, suggesting that termination of convulsive SE is still critical in elderly patients.

On the other hand, elderly people are more susceptible to the adverse effects of AEDs than are younger people [18]. Hypoventilation, hypotension and cardiac rhythm disturbance are major emergent adverse events of intravenous DZP, MZP and lorazepam (not
licensed in Japan) [19], and these adverse events easily lead to critical conditions in elderly patients. To avoid severe adverse effects, medications other than intravenous DZP, MZP or lorazepam are taken into consideration. In Japan, diazepam rectal gel, intramuscular MDZ, buccal MDZ, nasal MDZ, nasal lorazepam and buccal clonazepam have not been approved by the Ministry of Health, Labor and Welfare. In the current study, DZP supp was used in 6 of the 11 patients with SE. The dose of DZP supp used was smaller than the recommended dose of 15-20 mg for diazepam rectal gel [20]. Although SE was sustained for rather long periods, SE was terminated without using a ventilator or tracheal intubation in our patients. Both lower incidence of serious adverse effects and increased efficacy in stopping seizures with diazepam rectal gel have been reported in adult patients with acute repetitive seizures and prolonged seizures [21, 22]. Costs and medical resources for intensive care also should be taken into consideration. Comparative studies of aggressive treatment and milder treatment are necessary to evaluate the superiority of treatments for SE in elderly patients.

Conflict of interest
The authors declare that there are no conflicts of interest associated with this report.

References
[1] Sillanpää M, Lastunen S, Helenius H, Schmidt D. Regional differences and secular trends in the incidence of epilepsy in Finland: A nationwide 23-year registry study. Epilepsia 2011;52:1857-67.
[2] Brodie MJ, Elder AT, Kwan P. Epilepsy in later life. Lancet Neurol 2009;8:1019-30
[3] Sung CY, Chu NS. Status epilepticus in the elderly: etiology, seizure type and outcome. Acta Neurol Scand 1989;80:51-6.
[4] Fisher RS, Acevedo C, Arzimanoglou A, Bogacz A, Cross H, Elger CE, Engel Jr J, Forsgren L, French JA, Glynn M, Hesdorffer DC, Lee BI, Mathern GW, Moshé SL, Perucca E, Scheffer IE, Tomson T, Watanabe M, Wiebe S. A practical clinical definition of epilepsy. Epilepsia 2014;55:475-82.
[5] Beghi E, Carpio A, Forsgren L, Hesdorffer DC, Malmgren K, Sander JW, et al. Recommendation for a definition of acute symptomatic seizure. Epilepsia 2010;51:671-5.
[6] Walker M, Cross H, Smith S, Young C, Aicardi J, Appleton R, Aylett S, Drislane F, Duncan J, Ferrie C, Fujikawa D, Gray W, Kaplan P, Koutroumanidis M, O'Regan M, Plouin P, Sander J, Scott R, Shorvon S, Treiman D, Wasterlain C, Wieschmann U. Nonconvulsive status epilepticus: Epilepsy Research Foundation workshop reports. Epileptic Disord 2005;7:253-96.
[7] Treatment of convulsive status epilepticus. Recommendations of the Epilepsy Foundation of America's Working Group on Status Epilepticus. JAMA 1993;270:854-9.
[8] Berg AT, Berkovic SF, Brodie MJ, Buchhalter J, Cross JH, van Emde Boas W, Engel J, French J, Glauser TA, Mathern GW, Moshé SL, Nordli D,
Plouin P, Scheffer IE. Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology, 2005-2009. Epilepsia 2010;51:676-85.

[9] Statistics Bureau, Ministry of Internal Affairs and Communications website, Japan.  http://www.stat.go.jp/data/nihon/02.htm

[10] Faught E, Richman J, Martin R, Funkhouser R, Foushee R, Kratt P, Kim Y, Clements K, Cohen N, Adoboe D, Knowlton R, Pisu M. Incidence and prevalence of epilepsy among older US Medicare beneficiaries. Neurology 2012;78:448-53.

[11] Liu S, Yu W, Lü Y. The causes of new-onset epilepsy and seizures in the elderly. Neuropsychol Dis Treat 2016;12:1425-34.

[12] Stephen LJ, Brodie MJ. Epilepsy in elderly people. Lancet 2000;355:1441-46.

[13] Dam AM, Fuglsang-Frederiksen A, Svarre-Olsen U, Dam M. Late-onset epilepsy: etiologies, types of seizure, and value of clinical investigation, EEG, and computerized tomography scan. Epilepsia 1985;26(3):227-31.

[14] Sung CY, Chu NS. Status epilepticus in the elderly: etiology, seizure type and outcome. Acta Neurol Scand 1989;80:51-6.

[15] Shorvon SD, Baulac M, Cross H, Trinka E, Walker M, Taskforce on Status Epilepticus of the ILAE Commission for European Affairs. The drug treatment of status epilepticus in Europe: consensus document from a workshop at the first London Colloquium on Status Epilepticus. Epilepsia 2008;49:1277-85.

[16] Trinka E, Cock H, Hesdorffer D, Rossetti AO, Scheffer IE, Shinnar S, Shorvon S, Lowenstein DH. A definition and classification of status epilepticus - Report of the ILAE Task Force on Classification of Status Epilepticus. Epilepsia 2015;56:1515-23.

[17] Silveira DC, Jehl I, Chapin J, Krishnaiengar S, Novak E, Foldvary-Schaefer N, Najm I. Seizure semiology and aging. Epilepsy Behav 2011;20:375-7.

[18] Brodie MJ, Kwan P. Epilepsy in elderly people. BMJ 2005;331:1317-22.

[19] Glause T, Shinnar S, Gloss D, Allerdridge B, Arya R, Bainbridge J, Mare M, Bleck T, Dodson E, Garrity L, Jagoda A, Lowenstein D, Pellock J, Riviello J, Sloan E, Treiman DM. Evidence-based guideline: treatment of convulsive status epilepticus in children and adults: report of the guideline committee of the American Epilepsy Society. Epilepsy Curr 2016;16:48-61.

[20] Diastat R [package insert]. San Diego, CA: Xcel Pharmaceuticals; 2003

[21] Cereghino JJ, Mitchell WG, Murphy J, Kriel RL, Rosenfeld WE, Trevathan E, The North American Diastat Study Group. Treating repetitive seizures with a rectal diazepam formulation. A randomized study. Neurology 1998;51:1274-82.

[22] Fakhoury T, Chumley A, Bensalem-Owen M. Effectiveness of diazepam rectal gel in adults with acute repetitive seizures and prolonged seizures: a single
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-center experience. Epilepsy Behav 2007;11:357-60.