Presentation and management of community-onset vs hospital-onset first seizures

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Abstract

Background

New-onset seizures are frequently encountered in community and hospital settings. It is likely that seizures presenting in these distinct settings have different etiologies and prognoses, requiring different investigation and treatment approaches. We directly compare the presentation and management of patients with community- and hospital-onset first seizures attending the same hospital.

Methods

We reviewed the medical records of patients aged 18 years or older with discharge *International Classification of Diseases, Australian Classification (ICD-10-AM)* codes of G40 (epilepsy), G41 (status epilepticus), and R56.8 (unspecified convulsions), who attended a general hospital in Melbourne, Australia, from January 1, 2008, through November 30, 2016. Patients with new-onset seizures were included for analysis.

Results

A total of 367 patients were discharged with a relevant *ICD-10-AM* code. Among them, 151 patients met the inclusion criteria: 97 presented to the emergency department with community-onset seizure (median age 70 years), and 54 experienced seizures during hospitalization for other indications (median age 80.5 years). Provoked seizures were more common in the latter group (26.8% vs 63.0%, $p < 0.001$), with exposure to proconvulsant drugs a major risk factor. Despite not fulfilling the International League Against Epilepsy (ILAE) diagnostic criteria, 72.5% (58/80) who survived to discharge were prescribed antiepileptic drug (AED) therapy, whereas 19.0% (12/63) of those who met the ILAE criteria were not.

Conclusions

Hospitalized elderly patients are at an increased risk of provoked seizures, and caution should be exercised when prescribing potential proconvulsant medications and procedures. A more standardized approach to AED prescribing is needed. Further studies should consider morbidity, mortality, and health economic effects of first seizures and assess optimal management to improve outcomes in this cohort.

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Seizures are a common neurologic presentation in both community and hospital settings. Up to 10% of people have at least 1 seizure in their lifetime.¹ Seizures account for 1%–2% of emergency department (ED) visits^{2,3} and occur in 3.6% of hospitalized patients.⁴

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It is likely that new-onset or newly diagnosed seizures occurring in the community and during hospitalization for nonseizure illnesses have different etiologies and prognoses, thus requiring different investigation and treatment approaches. Previous studies have tended to investigate these cohorts separately, suggesting distinct demographic and treatment patterns. Patients with community-onset seizures (COS) presenting to EDs were reported to be men, in their mid-20s to mid-30s, have generalized convulsions, and be discharged directly home from the ED with almost half prescribed antiepileptic drugs (AEDs).^{3,5} Another study found that patients with hospital-onset seizures (HOS) tended to be men, in their 50s and 60s, have generalized convulsions, and two-thirds were prescribed AEDs at discharge.⁶

Direct comparison of patient characteristics between these studies is difficult owing to the different study settings. We compared the clinical presentation and management of COS and HOS within the same hospital.

Methods

Setting

This was a retrospective study of patients managed at Cabrini Malvern Hospital, Melbourne, Australia, between January 1, 2008, and November 30, 2016. The hospital is one of the major general private hospitals in metropolitan Melbourne with a 24/7 ED service. The hospital provides in- and out-patient neurology services including neurophysiology investigations. Medical charts of eligible patients were examined by 2 independent reviewers to extract information on patient demographics and clinical characteristics using a standardized proforma.

Standard protocol approvals, registrations, and patient consents

The study was approved by the hospital's Human Research Ethics Committee (study number 02-23-01-17).

Patients

Patients with new-onset or newly recognized seizures were identified by reviewing the medical records of consecutive patients who presented to the hospital's ED (COS group) or

had seizures during admission to the inpatient wards for other indications (HOS group), with subsequent discharge *International Classification of Diseases*, Australian Classification (ICD-10-AM) codes that included G40 (epilepsy), G41 (status epilepticus), and R56.8 (unspecified convulsions). Patients were eligible for inclusion if they were aged 18 years or older, did not have a previous diagnosis of epilepsy, and were not taking AED therapy when the seizure occurred. Patients were excluded if the presenting episode was attributed to an alternative diagnosis, also captured by R56.8, i.e., vasovagal syncope or a psychogenic nonepileptic event.

Definitions

Seizures were classified as provoked (acute symptomatic)⁷ or unprovoked⁸ according to International League Against Epilepsy (ILAE) guidelines. The former included seizures occurring within 1 week of a brain insult, within 24 hours of severe metabolic derangement, or in the context of excessive alcohol intake or exposure to well-defined proconvulsant drugs.^{9,10} Epilepsy was diagnosed based on the presence of 2 or more unprovoked seizures or 1 seizure with enduring risk of seizure occurrence of >60%.¹¹ Risk assessment was based on the history of previous brain insult, epileptiform abnormality on EEG, and epileptogenic lesion identified on brain imaging¹² (appendix e-1, links.lww.com/CPJ/A51). Epilepsy syndromes and seizure types were classified according to the latest ILAE schemes.^{13,14}

Data availability

Anonymized data, and the standardized proforma used to extract information on patient demographics and clinical characteristics, will be shared by request from any qualified investigator.

Statistical analysis

The Fisher exact test was performed to compare categorical variables. The Mann-Whitney *U* test was used to compare continuous variables. Odds ratios (ORs) for diagnostic results and commencement of AED therapy in the 2 groups were calculated. All statistical tests were performed by using Stata14 (StataCorp, College Station, TX). Statistical significance level of 0.05 was used unless otherwise specified. Bonferroni correction was applied for multiple testing.

Results

Patient characteristics

A total of 367 patients were discharged with one of the relevant ICD-10-AM codes. Among them, 151 patients met the inclusion criteria as having had new-onset or newly recognized seizures. Their median age was 74 years (interquartile range [IQR] 55–83 years). Fifty-two patients were aged <65 years (40 in the HOS group and 12 in the COS group). Eighty-four (55.6%) were women. The remaining 216 were excluded: 186 had a preexisting epilepsy diagnosis and 30 had nonseizure final diagnoses (figure 1).

Among the 151 patients included, 97 presented to the ED (COS group) and 54 experienced seizures during

Figure 1 Study flowchart for inclusion of patients into the final analysis

hospitalization for other indications (HOS group). Their baseline characteristics are shown in table 1. The HOS group was older (median age 80.5 years, IQR 67.3–85.3) than the COS group (median age 70 years, IQR 53–81.3, $p = 0.012$). There were no differences in sex distribution or presence of medical comorbidities (table 1).

Seizure characteristics and etiologies

A larger proportion of seizures in the HOS group were classified as provoked (acute symptomatic) compared with the COS group (63.0% vs 26.8%, $p < 0.001$). The difference was largely driven by exposure to proconvulsant drugs in the HOS group (38.9% vs 4.1% in the COS group, OR = 14.8,

Table 1 Patient baseline characteristics

	COS group, n (%) Total, n = 97	HOS group, n (%) Total, n = 54	<i>p</i> Value ^a
Patient characteristics			
Median age, y (IQR)	70	80.5	0.012
Females	54 (55.7)	30 (55.6)	>0.99
Medical comorbidities			
Any medical illness	84 (86.6)	51 (94.4)	0.17
Cardiovascular risk factors and conditions (ischemic heart disease, hypertension, stroke, diabetes, and obesity)	45 (46.4)	34 (63.0)	0.062
Respiratory condition (emphysema, chronic bronchitis, and asthma)	8 (8.3)	6 (11.1)	0.57
Inflammatory condition (dermatitis and arthritis)	11 (11.4)	7 (13.0)	0.80
Cancer (hematologic, skin, and solid cancers)	30 (30.9)	20 (37.0)	0.47
Gastric disease (peptic ulcer disease and liver condition)	1 (1.0)	0 (0)	>0.99

Abbreviations: COS = community-onset seizures; HOS = hospital-onset seizures; IQR = interquartile range.

^a After Bonferroni correction, statistical significance of p value = 0.0167 was used for age, sex, and any medical illness; p value = 0.01 was used for the 5 medical illness subcategories.

95% confidence interval [CI] 4.45–62.4, $p < 0.001$), most commonly the perioperative use of tranexamic acid (table 2) in cardiothoracic surgery, neurosurgery, and prostatectomy. Remote seizure risk factors were identified in 31/97 (32.0%) of the COS group and 11/54 (20.4%) of the HOS group ($p = 0.14$), most frequently cerebral lesion(s) (table 2). The majority of seizures were recorded as convulsive (84/97 [86.6%] in the COS group and 48/54 [88.9%] in the HOS group). There was no difference in the occurrence of convulsive and nonconvulsive seizures between the 2 groups. Status epilepticus occurred in 4/97 (4.1%) of the COS group and 3/54 (5.5%) of the HOS group.

The majority of patients underwent cerebral imaging, including CT, MRI, or both ($n = 89/97$, 91.8% COS and 44/54, 81.5% HOS groups) (table 2). Epileptogenic lesions were detected in 39/89 (43.8%) of the COS group and 8/44 (18.2%) of the HOS group (OR = 3.51, 95% CI 1.39–9.67, $p = 0.004$). MRI identified lesions that CT did not detect in 5/42 (11.9%) of the COS group and 1/15 (6.7%) of the HOS group ($p > 0.99$). Approximately half of the patients in both the COS and HOS groups underwent EEG, detecting epileptiform abnormalities in a similar proportion of patients (18.0% and 17.9%, respectively).

Inpatient management and outcome

The majority of patients in the COS group were admitted as inpatients under various specialties including neurology (56/97 [57.7%]), general medicine (17/97 [17.5%]), and oncology (11/97 [11.3%]). Patients in the HOS group were admitted under specialties including cardiothoracic surgery (18/54 [33.3%]), general medicine (14/54 [25.9%]), oncology (5/54 [9.3%]), and neurology (3/54 [5.6%]).

Forty-five patients were admitted to the intensive care unit (ICU) (14 in the COS group and 31 in the HOS group, $p < 0.001$). Mortality was higher in the ICU group (13.3% [6/45]) than in the non-ICU group (1.9% [2/106], OR = 8.00, 95% CI 1.34–83, $p = 0.004$). There were similar rates of seizure recurrence and epileptiform abnormalities for those who underwent EEG.

An IV loading dose of phenytoin was more commonly administered to the HOS group (36/54 [66.7%]) compared with the COS group (37/97 [38.1%], OR = 3.24, 95% CI 1.53–6.96). Seizure recurrence during hospitalization was more common in the HOS group (14/54 [25.9%]) compared with the COS group (7/97 [7.2%], OR = 4.50, 95% CI 1.54–14.1). Most patients (80.4%) originally admitted under non-neurology specialties received in-patient neurology review after the seizure. Among patients who fulfilled the epilepsy diagnostic criteria ($n = 63$), the proportion initiated on AED therapy was similar between those who had neurology consultation and those who did not. Of patients surviving to discharge, those with COS were more likely to fulfill the ILAE diagnostic criteria compared with

Although guidelines provide general recommendations, ultimately the risks and benefits of initiating AED therapy need to be tailored to the individual patient.

those with HOS (53/93 [57.0%] and 10/50 [20.0%], respectively, OR = 5.30, 95% CI 2.24–13.2, $p < 0.001$) (figure 2). A similar proportion of patients surviving to discharge were prescribed AED in each group (69/93 [74.2%] in the COS group and 40/50 [80.0%] in the HOS group). Of those prescribed AEDs, 65.0% of COS and 80.0% of HOS group patients did not fulfill the ILAE diagnostic criteria. Conversely, one-fifth of both groups who fulfilled the ILAE diagnostic criteria did not receive an AED prescription on discharge (10/53 [18.9%] of the COS group and 2/10 [20.0%] of the HOS group).

Phenytoin was the most common discharge AED in both groups (19/93 [20.4%] COS and 26/50 [52.0%] HOS groups), followed by valproate (15/93 [16.1%] COS and 5/50 [10.0%] HOS groups); several patients were prescribed multiple AEDs at discharge ($n = 5/93$ [5.4%] COS and $n = 2/50$ [4.0%] HOS groups). Table 3 includes all those with status epilepticus who survived to discharge (3 of the COS group and 2 of the HOS group).

Four patients from each group (4/97 [4.1%] of the COS group and 4/54 [7.4%] of the HOS group, OR = 0.54, 95% CI 0.10–3.03) died during hospitalization or were transferred to a hospice. All deaths were expected. Causes of death included intracranial hemorrhage, anoxic brain damage, metastatic cancer, and sepsis.

Discussion

This study reveals clear differences in characteristics between patients presenting after new-onset seizures occurring in the community and those that occurred during hospitalization for non-seizure-related illnesses. The latter group were older and more likely to have acute symptomatic seizures, whereas those with COS were more likely to be diagnosed with new-onset epilepsy, yet a similar proportion of patients in each group were prescribed AED therapy on discharge.

As noted in previous studies, the HOS group was significantly older than the COS group. A provoking etiology was identified in over half the HOS group, with exposure to pro-convulsant drugs, most commonly tranexamic acid, the major causative drug. The rate of provoked seizures in the HOS group was higher (63.0%) than the 20%–50% previously

Table 2 Seizure characteristics and investigations undertaken

	COS group, n (%) Total, n = 97	HOS group, n (%) Total, n = 54	<i>p</i> Value ^a
Seizure semiology			0.91
Nonconvulsive (including FAS and FIAS)	11 (11.3)	5 (9.3)	
Convulsive (including FAS, FIAS, focal to BL TCS, and GTCS)	84 (86.6)	48 (88.9)	
Unknown	2 (2.1)	1 (1.9)	
Acute symptomatic seizure risk factors	26 (26.8)	34 (63.0)	<0.001
Stroke (ischemic or hemorrhagic)	5 (5.2)	5 (9.3)	0.33
Anoxic encephalopathy	2 (2.1)	2 (3.7)	0.62
Intracranial surgery	1 (1.0)	3 (5.6)	0.13
Subdural hemorrhage (at first identification)	4 (4.1)	1 (1.9)	0.66
Active CNS infection	2 (2.1)	0 (0)	0.54
Autoimmune lymphoproliferative disorder	1 (1.0)	0 (0)	>0.99
Severe metabolic derangements	2 (2.1)	1 (1.9)	>0.99
Drug and/or alcohol withdrawal	5 (5.2)	1 (1.9)	0.42
Exposure to epileptogenic drugs	4 (4.1)	21 (38.9)	<0.001
Remote seizure etiologies	31 (32.0)	11 (20.4)	0.14
Mesial temporal sclerosis	1 (1.0)	0 (0)	>0.99
Primary CNS tumor	7 (7.2)	2 (3.7)	0.49
Cerebral metastases	14 (14.4)	5 (9.3)	0.45
Gliosis/encephalomalacia	7 (7.2)	3 (5.6)	>0.99
Severe head trauma	1 (1.0)	1 (1.9)	>0.99
Vascular anomaly	1 (1.0)	0 (0)	>0.99
Investigations			
CT and/or MRI performed	89 (91.8)	44 (81.5)	0.071
Epileptogenic abnormality	39/89 (43.8)	8/44 (18.2)	0.004
EEG performed	48 (50.5)	28 (51.9)	0.87
Epileptiform activity	9/48 (18.0)	5/28 (17.9)	>0.99
CSF analysis performed	8 (9.3)	6 (9.3)	0.57
Viral infection identified	1/8 (12.5)	0/6 (0)	>0.99
Malignant cells identified	0/8 (0)	2/6 (33.31)	0.17
Met ILAE diagnosis	54 (55.7)	12 (22.2)	<0.001
Two or more unprovoked seizures occurring more than 24 h apart	19 (19.6)	7 (13.0)	0.37
One unprovoked seizure and increased risk of further seizures	33 (34.0)	5 (9.3)	0.001
Diagnosis of an epilepsy syndrome	2 (2.1)	0	0.54

Abbreviations: BL TCS = bilateral tonic clonic seizure; COS = community-onset seizures; FAS = focal aware seizure; FIAS = focal impaired awareness seizure; GTCS = generalized tonic-clonic seizure; HOS = hospital-onset seizures; ILAE = International League Against Epilepsy.

^a After Bonferroni correction, statistical significance of *p* value = 0.0071 was used for the 7 main seizure characteristics and investigations, *p* value = 0.0056 was used for 9 subcategories of acute symptomatic seizure risk factors, *p* value = 0.0083 for 6 subcategories of remote seizure etiologies, *p* value = 0.025 for 2 subcategories of CSF analysis, and *p* value = 0.0167 for 3 subcategories of ILAE diagnosis.

Figure 2 Rates of AED prescription correlated with ILAE diagnostic criteria for the COS and HOS groups

reported.^{15,16} This may reflect lower seizure thresholds in an older, hospitalized patient population that has increased susceptibility to acute brain insults. The association between tranexamic acid and an increased incidence of seizures, particularly during the early postoperative period after cardiac surgery, is well described.¹⁷ This was strongly supported in our study, with 27.8% of the HOS group having received tranexamic acid in the period around cardiac surgery. Strategies to reduce the risk of tranexamic acid-associated seizures should be considered, including the use of reduced

dosage and continuing the general anesthetic agent for several hours after a surgical procedure, if safe and practicable to do so.¹⁰

In contrast, the majority of the COS group had no identifiable acute provoking factors but had higher rates of remote seizure risk factors. The most commonly identified remote seizure risk factor was cerebral lesions, including structural brain damage from ischemic strokes, and primary and metastatic cerebral cancers. This is consistent with findings from a study that reported stroke and tumors as the underlying seizure etiology for 23% and 9% of patients hospitalized with first-ever seizures, respectively.⁶

Hauser et al.¹⁸ reported that the highest incidence of epilepsy occurred in people older than 75 years. This may explain the high rates of new epilepsy diagnosis in our elderly cohort with almost three-fifths of COS and one-fifth of HOS groups fulfilling the ILAE diagnostic criteria. The decision to initiate AED therapy is complex and needs to consider patient preference, medical comorbidities, concomitant medications, and specific epilepsy syndrome or presenting seizure type(s).^{19–21} AED therapy is generally recommended for those with an enduring propensity for further seizures (i.e., fulfilling the ILAE diagnostic criteria). Conversely, AED therapy is not indicated in those with acute symptomatic seizures, which have a low risk of recurrence.²² AED therapy was initiated in over four-fifths of patients with newly diagnosed epilepsy. Similar prescribing patterns were noted in a Swedish population-based registry: 85.1% of patients with newly diagnosed epilepsy were prescribed AED therapy within the first year after the index seizure.²³ Conversely, 65% of COS and 80% of HOS patients without newly

Table 3 Antiepileptic drug choice for each group on discharge

	COS group, n (%) Alive at discharge Total, n = 93	HOS group, n (%) Alive at discharge Total, n = 50
None	24/93 (25.8)	10/50 (20.0)
PHT	19/93 (20.4)	26/50 (52.0)
VPA	15/93 (16.1)	5/50 (10.0)
LEV	14/93 (15.1)	4/50 (8.0)
CBZ	16/93 (17.2)	3/50 (6.0)
PHT + VPA	2/93 (2.2)	1/50 (2.0)
PHT + LEV	1/93 (1.1)	1/50 (2.0)
PHT + CBZ	1/93 (1.1)	0
PHT + LEV + VPA	1/93 (1.1)	0

Abbreviations: CBZ = carbamazepine; COS = community-onset seizures; HOS = hospital-onset seizures; LEV = levetiracetam; PHT = phenytoin; VPA = valproate.

diagnosed epilepsy were also prescribed AED therapy. The decision to prescribe or not to prescribe requires careful balancing of the risk of missed opportunities for initiation and titration of appropriate therapy against the risk of overtreatment with potential side effects and drug-drug interaction. This study highlights the complexity of clinical practice: although guidelines provide general recommendations, ultimately the risks and benefits of initiating AED therapy need to be tailored to the individual patient.

Phenytoin was the commonest AED monotherapy prescribed at discharge. This prescribing behavior is consistent with previous US-based studies regarding seizure presentations to EDs³ and occurring in hospital.⁶ However, it differs from the Swedish population registry that reported carbamazepine as the most frequent initially prescribed AED.²³ The difference may reflect local prescribing habit. Phenytoin has many drug-drug interactions, a considerable side effect profile including the increased risk of osteoporosis and Stevens-Johnson syndrome, and requires regular blood tests to monitor drug levels and screen for organotoxicity.^{20,22} In this regard, phenytoin might not have been the most appropriate initial AED for our elderly study population, many of whom had comorbidities and were taking polypharmacy.

Patients in our study were older than those in other studies reporting on COS and HOS. This may reflect the older population in the hospital catchment area.²⁴ The majority of COS presenting to the ED were admitted to the ward. This is in keeping with previous Australian research⁵ that reported increased rates of seizure-related hospitalizations for patients aged >65 years, likely because of comorbidities occurring more frequently in the elderly, such as stroke and cancer.

Although the majority of new-onset seizures in the elderly are focal,²⁵ convulsive seizures were the most frequent presentation in both the COS and HOS groups. Our results are consistent with previous work demonstrating that first seizures are twice as likely to be generalized than focal.² One study reported that 86% of COS presenting to the ED were generalized convulsions³; another study found that generalized seizures were the commonest type in an HOS group.⁶ This bias toward generalized seizures might be because focal seizures are not readily brought to medical attention, as they are either not detected or not of sufficient concern to patients or bystanders. Conversely, generalized, convulsive seizures are more alarming and may prompt bystanders to rapidly involve emergency services.

Limitations

Limitations of this survey include its small study size, which reduces its power to determine ability for some tests, such as CSF analysis, to detect abnormalities. Long-term follow-up data, including data from other health services, were not

readily available. Efforts were made to minimize the effect on the validity of findings by reviewing all information within medical records including medical, nursing, and allied health notes; reviewing each patient's entire medical record from index seizure event through to most recent hospital episode; and review of correspondence from other health services. The retrospective nature of this survey carries inherent uncertainty with regard to exact diagnosis. However, a previous study found that external review of medical records has high specificity and sensitivity for diagnosis and determination of activity for new-onset seizure and new-onset epilepsy.²⁶ Diagnosis of any disease is based on contemporary guidelines. In 2014, the ILAE expanded epilepsy diagnostic criteria. Applying these updated diagnostic criteria to patients assessed before 2014 might have resulted in reclassification of more cases as newly diagnosed epilepsy. It is acknowledged that the bias toward older age and a private hospital setting may limit the generalizability of the results. However, those aged >65 years are most likely to develop new-onset seizures in high-income countries. This study therefore provides valuable insights into this specific demographic and hospital setting. Information regarding the duration of AED therapy was not available, and prescription at discharge, especially for those with provoked seizures, may have been short-term therapy to cover an "at-risk" period. EEG rates were less than expected. We speculate that EEG might have been omitted because of lack of availability outside business hours, for patients with obvious acute symptomatic seizures, and for extremely frail patients nearing palliation, on the basis that results would be low yield or not change overall prognosis and management.

Conclusion

Elderly hospitalized patients are at an increased risk of provoked seizures. Due care should be exercised when prescribing potentially proconvulsant medications for this group. We highlight particularly the seizure risks associated with tranexamic acid, especially in the context of cardiac surgery. AED prescription decisions at discharge revealed the complexities of clinical practice, with factors beyond new-diagnosis epilepsy likely influencing decisions regarding AED initiation. Further study is needed into patient and seizure characteristics for new-onset or newly recognized seizures that occur in the community compared with those that occur in patients already hospitalized for nonseizure illnesses to help guide hospital policies and ensure the appropriate use of hospital and community health resources. Further studies should also consider morbidity, mortality, and health economic effects of first seizures and assess optimal management to improve outcomes in this cohort.

Author contributions

E. Foster: conception of the manuscript, collection of data, preparation of the manuscript, and critical revision of the

manuscript for intellectual content. S. Holper: collection of data and critical revision of the manuscript for intellectual content. Z. Chen: statistical analysis. P. Kwan: conception of the manuscript and critical revision of the manuscript for intellectual content.

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Practical Implications

Neurology® Clinical Practice is committed to providing clinical insights helpful to neurologists in everyday practice. Each Full Case includes a “Practical Implications” statement, a pearl of wisdom for the practicing clinician.