Hospital-Onset Seizures

An Inpatient Study

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Objectives: To describe demographic and clinical characteristics of patients with hospital-onset seizure (HOS) and to explore current practices in their management.

Design: Retrospective medical record review.

Setting: Academic, tertiary care, private (New York University Langone Medical Center) and municipal (Bellevue Hospital Center) medical centers.

Patients: Patients aged at least 18 years with HOS from January 1 through December 31, 2007. Patients admitted for evaluation of seizures or epilepsy were excluded.

Main Outcome Measures: Hospital-onset seizure patterns, medication use, and outcomes.

Results: We identified 218 patients with HOS; 139 (64%) had no history of seizure. Hospital-onset seizures were recurrent in 134 patients (61%) during the inpatient stay and were more likely to recur in those with new-onset seizure vs those with a history of seizure (43% vs 32%, \( P = .09 \)). The most commonly described HOS in patients with a history of seizure and patients with new-onset seizure was a generalized tonic-clonic seizure (72 [33%]). Metabolic derangements were the most common identifiable cause of HOS (43 of 218 [20%]) and new-onset seizures (35 of 139 [25%]) and were more likely to recur. Phenytoin was the most common antiepileptic drug prescribed de novo (61%). Death during hospitalization or discharge to hospice was more common in patients with new-onset seizures compared with those with a history of seizure (19% vs 5%, \( P = .004 \)). Among surviving patients discharged with a prescription of antiepileptic drugs, phenytoin and levetiracetam were prescribed most often.

Conclusions: Hospital-onset seizures commonly occur as new-onset seizures, are typically recurrent, and are associated with a high mortality. Older antiepileptic drugs are often prescribed at seizure presentation and at discharge.

therapy in the hospital is evolving. Newer AEDs are increasingly used in outpatient settings and have been particularly recommended for patients with medical comorbidities owing to higher risk of drug interactions, concern about adverse drug reactions, and issues of protein binding associated with the older AEDs.7,8 Yet, at least in other countries where some epidemiologic studies9,10 have been performed, older AEDs apparently are the preferred first-line therapy for HOS.

The incidence of HOS, the circumstances of these seizures, the setting in which they occur, the treatments used, and the impact of AEDs is currently unknown. The purpose of this study was to describe demographic and clinical characteristics of patients with HOS and to explore current practices in their management. We studied 2 separate hospitals affiliated with the New York University (NYU) School of Medicine: NYU Langone Medical Center, a private nonprofit hospital, and Bellevue Hospital Center, a large municipal hospital.

METHODS

This was a retrospective study conducted through medical record review. Hospital discharges from January 1 through December 31, 2007, with the following characteristics were screened for HOS: (1) discharge with primary or secondary International Classification of Diseases, Ninth Revision (ICD-9) codes 780.3x and 345.xx or (2) inpatient treatment with the most commonly prescribed AEDs (levetiracetam, phenobarbital sodium, valproic acid, and loading doses of phenytoin sodium/ fosphenytoin sodium). Pharmacy data were used to capture patients with HOS missing a discharge ICD-9 code for seizures or epilepsy. Inclusion criteria were age at least 18 years, medical record confirmation of inpatient seizure, and for patients found through pharmacy screening, receipt of AEDs for HOS.

Exclusion criterion was admission for seizures or epilepsy.

Seizures were identified on the basis of notes written by attending physicians, residents, and nurses. Seizures were then classified according to the International League Against Epilepsy classification11 when possible. Seizures were given the designation “unknown” when the semiology of the attack could not be clearly ascertained or was not described in the notes.

Relevant variables extracted from medical records included demographic data, admission date, discharge date, underlying medical conditions, location and service at the time of the seizure(s), incident seizure information, and laboratory data.

Metabolic derangements were defined as a serum glucose level less than 36 mg/dL or greater than 450 mg/dL (to convert to millimoles per liter, multiply by 0.0555), serum sodium less than 115 mEq/L (to convert to millimoles per liter, multiply by 0.0555), serum calcium less than 5.0 mg/dL (to convert to millimoles per liter, multiply by 0.25), serum magnesium less than 0.4 mEq/L (to convert to millimoles per liter, multiply by 0.25), serum creatinine greater than 10.0 mg/dL (to convert to micromoles per liter, multiply by 0.0555), urea nitrogen less than 100 mg/dL (to convert to millimoles per liter, multiply by 0.357), and creatinine greater than 10.0 mg/dL (to convert to micromoles per liter, multiply by 88.4).12 Medications administered during the hospitalization, including AEDs, antibiotics, statins, immunosuppressants, and anticoagulants, were noted.

Statistical comparisons were made with Mantel-Haenszel, \( \chi^2 \), Fisher exact, or Wilcoxon rank sum test.

RESULTS

We screened 3345 medical records of patients who had an ICD-9 code of epilepsy or seizure or who were identified from pharmacy data in 2007. Most were excluded because they did not have HOS or were admitted for evaluation of a seizure or epilepsy. One hundred twelve patients met inclusion criteria at NYU Langone. Consecutive medical records were reviewed from Bellevue and an additional 106 eligible patients were identified for a total of 218 with confirmed HOS. Discharge ICD-9 codes identified 75% of the patients at Bellevue and 91% at NYU. The rest were identified through pharmacy review. Demographic data broken down by hospital can be seen in Table 1.

New-onset seizures occurred in 139 patients (64%), whereas 79 (36%) had a history of seizure. Status epilepticus occurred in 18 patients (8%); for 12 (6%), this was the index seizure. Of the 79 patients with history of seizure, 19 (24%) had not had a seizure in the year prior to admission. Status epilepticus occurred in 9 of the 139 patients (6%) with new-onset seizures and 9 of the 79 (11%) with a history of seizure.

A single seizure occurred in 84 patients (39%), while 49 (22%) had multiple seizures during a single day and 85 (39%) had seizures on multiple days. Patients with new-onset seizures tended to be more likely to have recurrent seizures than patients with epilepsy (43% vs 32%, \( P = .09 \)).
SEMILOGY

Semiology was determined by the description in the medical record note. The most common description of HOS was generalized tonic-clonic convulsions (72 [33%]), followed by complex partial seizures (45 [21%]). This was true for patients with new-onset seizures and those with a history of epilepsy (Table 2).

ETIOLOGY

Stroke, metabolic derangement, and brain tumor were the most common identifiable etiologies. No single etiology predominated as the cause of HOS. Table 3 lists the etiologies for the patients with and without prior seizures. There was no predominant etiology among those with a history of seizure. The most common identifiable cause of HOS in the 133 patients with seizures on just a single day was stroke (23 [17%]). In the 85 patients with seizures on recurrent days, the most common identifiable cause was metabolic abnormalities (21 [25%]).

SERVICE AND LOCATION

Patients with HOS were not housed primarily on neurology services (Table 4). The most common service was medicine (59%). The most common location was non-ICU inpatient service (123 [56%]), followed by the ICU (71 [33%]) and the emergency department (24 [11%]). Patients with no history of epilepsy were more likely to be in the ICU at the time of their index seizure (39% vs 22%, \(P = .009\)).

TREATMENT

One hundred thirty-eight patients were not receiving an AED at the time of their first seizure. In the 79 patients with a history of seizure, 16 (20%) were not receiving an AED before hospitalization and 31 (39%) were receiving 2 or more AEDs. The most common AEDs before hospitalization were levetiracetam (33 [52%]), phenytoin (21 [33%]), and valproic acid (12 [19%]).

In the 130 patients who did not have a history of seizure or an index seizure that was status epilepticus, 17 (13%) were receiving AED prophylaxis at the time of their first seizure. Levetiracetam (7 [41%]) and phenytoin (5 [29%]) were the most common AEDs used for prophylaxis.

Benzodiazepines were used as initial seizure treatment in 132 patients (61%). Of the 12 patients with status epilepticus as their index seizure, 3 (25%) received benzodiazepines at the onset of their seizures.

The AEDs used to treat the index seizure in new-onset seizure patients were phenytoin (68 [49%]), levetiracetam (34 [24%]), and other drugs (12 [9%]). Thirteen new-onset seizure patients (9%) received no treatment, 11 (8%) had their prophylactic AED adjusted, and 1 (1%) had the prophylactic AED continued unchanged.

In the group with a history of seizure, treatment for the index HOS was phenytoin (22 [28%]), increase in the baseline AED (19 [24%]), continuation of the baseline AED without change (16 [20%]), levetiracetam (10 [13%]), other drugs (9 [11%]), or no AED (3 [4%]).

During the entire hospital stay, phenytoin was used more commonly in new-onset seizure patients than those with prior epilepsy (61% vs 38%, \(P = .002\)). Likelihood of selection of phenytoin vs other drug use did not vary with age, seizure etiology, underlying medical condition, service at time of index seizure, or seizure occurrence in an ICU.

Phenytoin was not always used in a manner consistent with current standards. The intravenous phenytoin loading dose that was selected translated to a weight-based dose ranging from 3.3 to 37.4 mg/kg (standard suggested urgent dose, 15-20 mg/kg). The dose that was ordered for an intravenous phenytoin load was often not individualized (1 g in 66% of patients). A post-
load phenytoin level, when corrected for albumin (measured phenytoin level / [(0.2 × albumin) + 0.1]), was therapeutic in 44 patients (42%), subtherapeutic in 22 (21%), supratherapeutic in 9 (9%), and not checked in 30 (29%).

OUTCOME

Death or discharge to hospice was common, occurring in 31 patients (14%). Most of the deaths or hospice discharges occurred in new-onset seizure patients (27 [19%] vs 4 [5%] with a history of epilepsy, P = .004). Death or discharge to hospice occurred in 15 of 71 patients (21%) who had a seizure in the ICU vs 16 of 147 patients (11%) who had their index seizure in other locations (P = .04). Death or discharge to hospice occurred more often in patients who experienced recurrent hospital seizures compared with those with a single seizure (18 of 85 [21%] vs 13 of 133 [10%], P = .02).

Among the 112 new-onset seizure patients who left the hospital, 38 (34%) were not discharged receiving an AED. Among new-onset seizure patients receiving AEDs on discharge, phenytoin was prescribed in 8 of 50 (16%) at NYU and 21 of 60 (35%) at Bellevue (P = .03). Overall, including patients with either new-onset seizure or a history of seizures, phenytoin was prescribed at discharge in 26% of patients leaving the hospital, which represented a 100% increase over the number who were receiving phenytoin at admission (13%). Levetiracetam was prescribed to 20% of all patients on admission to both hospitals and 52% of patients at discharge.

COMMENT

Hospital-onset seizures typically occur in seizure-naive patients and are therefore likely acute symptomatic in origin. Acute symptomatic seizures are clinical seizures occurring at the time of a systemic insult or in close temporal association with a documented brain injury.12-16

Patients, especially new-onset seizure patients, were likely to have more than 1 HOS, usually on multiple days without meeting criteria for status epilepticus. To our knowledge, this observation has never been reported and may be important for HOS management. Most seizures were discovered through clinical observation, and electroencephalography monitoring might well have uncovered even more. Electroencephalography monitoring has become more available and more frequently used in the hospital setting.17

No single etiology predominated as the cause of HOS. The most common identifiable cause of recurrent hospital seizures was metabolic derangements. However, hospitalization appears to pose a risk for epileptic patients because 24% were seemingly well controlled before entering the hospital. It appears that patients with an epilepsy history are not as ill as those with new-onset seizures (less likely to be in an ICU and less likely to die or to be discharged to hospice), and their seizures were more often self-limited. Patients with a history of seizure were also less likely to have recurrent HOS.

Twice the number of patients who entered the hospital receiving AEDs left the hospital receiving AEDs. Perhaps long-term drug selection (often phenytoin, a hepatic enzyme–inducing AED) was at times predicated on acute choice rather than consideration of the consequences of long-term therapy in what is most likely an ill population receiving concomitant medications whose metabolism could be affected by phenytoin.

Our data indicate that this is a population at risk for many reasons, including high risk of recurrence, high risk of death, and high potential for medication interactions. However, it is likely that death occurred as a direct consequence of the acuity of underlying illness, not as a result of seizure occurrence or medication choice. Moreover, our data suggest that the manner of drug use (at least for phenytoin) was not ideal. These findings underscore a need for further study in this area.

Our study was limited by the retrospective nature of the data acquisition. Moreover, we could not truly determine the incidence and prevalence of HOS owing to our study design. A prospective study might provide better information that could lead to improved health outcomes in these patients.

Another important corollary of the high risk of recurrent hospital seizures (and indeed one of the reasons for initiating this study) is that there is not only equipoise but also the capability to perform a randomized study comparing 2 treatments in this population. This study provides preliminary data that could be used to plan a randomized controlled trial. Seizure recurrence was common enough that it could be a primary outcome measure.

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| Table 4. Service at Seizure Onset for 218 Patients |
|-------------------|-------------------|-------------------|
| Service            | Frequency, No. (%) |
| Medicine           | 128 (59)          |
| Surgery            | 39 (18)           |
| Neurology          | 28 (13)           |
| Neurosurgery       | 23 (11)           |

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**Online-Only Material:** Listen to an author interview about this article, and others, at http://bit.ly/MT7xg4.

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### REFERENCES