Impact of seizures on morbidity and mortality after stroke: a Canadian multi-centre cohort study

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Introduction: Limited information is available about the impact of seizures on stroke outcome, health care delivery and resource utilization.
Objective: To determine whether the presence of seizures after stroke increases disability, mortality and health care utilization (length of hospital stay, ICU admission, consults, discharge to a long-term care facility).
Methods: This cohort study included consecutive patients with acute stroke between July 2003 and June 2005 from the Registry of the Canadian Stroke Network (RCSN), the largest clinical database of patients in Canada with acute stroke seen at selected acute care hospitals. We compared clinical characteristics and outcomes amongst patients experiencing stroke without and with seizures occurring during inpatient stay. Main outcome measures included: case-fatality, disability at discharge, length-of-stay, and discharge disposition. A logistic regression analysis was used to determine whether the presence of seizures was associated with poor stroke outcomes.
Results: Amongst 5027 patients included in the study; seizures occurred in 138 (2.7%) patients with stroke. Patients with seizures had a higher mortality at 30-day (36.2% vs. 16.8%, $P < 0.0001$) and at 1-year post-stroke (48.6% vs. 27.7%, $P < 0.001$), longer hospitalization, and greater disability at discharge ($P < 0.001$). Multivariate analysis revealed that stroke severity, hemorrhagic stroke, and presence of neglect were associated to occurrence of seizures after stroke.
Conclusions: The presence of seizures after stroke was associated with increased resources utilization, length of hospital stay, whilst decreasing both 30-day and 1-year survival. Quality improvement strategies targeting patients with seizures may help optimize the management of this subgroup of more disabled patients.

Introduction

Seizures are a common phenomenon after stroke, overall occurring in 2–20% of all patients with stroke [1–5]. On the other hand, it is well known that stroke is an important cause of epileptic seizures. Differences in the study design, definition of early or late seizures and post-stroke epilepsy, population target, inclusion and exclusion criteria, and imaging data, limit a direct comparison of these studies and may explain contradictory results in the literature [6–11]. Interestingly, not many studies have taken into account patients' and health system perspectives, particularly on resources utilization and impact of seizures on stroke outcome [12,13], We hypothesized that (i) the presence of seizures after stroke affects short and long-term stroke outcome, (ii) utilization of resources is higher in patients with seizures following a stroke, and (iii) the presence of seizures prolonged the hospital stay, thus affecting the discharge planning.

The aim of this study was to evaluate the impact of seizure occurrence in the outcome following stroke, in terms of mortality and morbidity, focusing on health-related services in the in- and out-patient setting, as well as to determine predictors of seizures after stroke.

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Methods

Participants/Population target and Registry of the Canadian Stroke Network

We identified all stroke patients admitted to Regional Stroke Centers in the province of Ontario, between 1 July 2003, and 30 June 2005 through the Registry of the Canadian Stroke Network (RCSN), warehoused at the Institute of Clinical Evaluative Sciences and managed by the Canadian Stroke Network (CSN).

The RCSN is a large clinical database of patients, with acute strokes seen at 11 acute care academic- and non-academic-based hospitals, with a current accrual rate of over 30 000 patients since its inception. All patients in this registry were identified prospectively and data were collected systematically during hospital stay and at the time of discharge with standard case report forms. A stroke neurologist served as a project leader at each site and trained neurology research nurses performed patient recruitment and data entry based on chart review and patient and family interviews. Patients with incomplete or missing clinical data, non-stroke diagnoses and transient ischaemic attacks were excluded.

Each patient in the RCSN is assigned a unique, encrypted identifier. Data were entered electronically, and the aggregate anonymous database was managed at the Institute for Clinical Evaluative Sciences in Toronto, Ontario. Further details of the RCSN have been published elsewhere [14–16].

Clinical variables and indicators

Stroke type was assessed as ischaemic or intracranial hemorrhage. Ischaemic stroke subtype was based on the Oxfordshire Community Stroke Project (OCSP) classification [17]; i.e. total anterior circulation infarct, partial anterior circulation infarct, posterior circulation infarct and lacunar infarct (LACI) [17]. Patients with transient ischaemic attacks were not included in the present study. Presenting symptoms were recorded in the case-report form.

The Charlson-Deyo index was used to quantify patients' comorbidities. This index is a summary score based on the presence or absence of 17 medical conditions. A score of zero indicates that no comorbidities are present, and higher scores indicate a greater burden of comorbidity. The Charlson-Deyo index was classified as having 0, 1, 2 or more than 3 comorbidities [18–20]. Stroke severity was assessed by using the Canadian Neurological Scale (CNS), as well as the NIH Stroke Scale (obtained upon admission to the hospital) [21,22]. The CNS is a simple, reliable and validated scale that gives a score (the lower the score the higher the severity) for estimating the acute neurological status [21,22]. Stroke unit was defined as a geographically located hospital unit with a dedicated stroke team and stroke resources (e.g. care pathway, educational materials, and monitored beds). This unit does not need to have all these resources nor does it have to be exclusively for stroke patients but it must be in one location in the hospital. Stroke team was defined as a multidisciplinary group of stroke specialists including neurologists, occupational therapists, physiotherapists, and speech language pathologists. Assessment by any of these allied health professionals was recorded in the RCSN as a visit at any point during the hospitalization. Pneumonia was included as a medical complication if it occurred within the first 30 days of the hospital stay and was confirmed radiologically. Length of stay (LOS) was defined as the number of days in the acute care facility from admission to discharge to the previous place of residence, rehabilitation institution or death.

Exposure: seizures were defined according to the International League Against Epilepsy as a paroxysmal disorder of the central nervous system with or without loss of consciousness or awareness, and associated or not with motor involvement [23] at any point since stroke onset or during the period of hospitalization. Decerebrate fits and limb-shaking TIA were not included in the present study. Moreover, there were other categories (checkboxes) to define other symptoms/diagnosis (e.g. vertigo, migraine) rather than seizures, according to the treating physicians. Even though we were not able to obtain an exact time and date of the seizure occurrence, all seizures that occurred during hospitalization because of stroke were taken into account.

Outcome measures

Stroke fatality was determined from the Ontario Registered Person database (RPDB), which contains vital statistics and cause of death in the province. This database was developed and is maintained by the Ontario Ministry of Health. The RPDB was used to confirm deaths recorded in the RCSN and to capture out-of-hospital deaths up to 1 year after discharge.

Thirty-days and 1-year case-fatality were defined as the proportion of strokes where death (regardless of cause) occurred within 30 days and 1 year of stroke admission respectively. These indicators have been extensively used in population-based studies and randomized clinical trials. We also analyzed disability at discharge, hospital LOS, and resources utilization. Outcome measures were compared between two groups: patients with and without seizures. Disability at discharge was measured by using the modified-Rankin scale [24]. Resources utilization included use of speech pathology, physical, and occupational therapy services.

Statistical analysis

Statistical analysis: chi-square tests were used to compare categorical variables; Student's *t*-tests and median two-sample tests were used for continuous variables. Logistic regression with backward selection models was developed to determine the relationship of the presence of seizures and stroke fatality. Other variables were considered for inclusion in the multivariable model if they were significant at the $P < 0.20$ level in the univariate analysis, to evaluate is the findings were related to a possible confounder effect.

Statistical analysis was performed using commercially available software package SAS statistical software (Version 9.1.3, Cary, NC: SAS Institute Inc.). All tests were two-tailed, and *P*-values <0.05 were considered significant.

Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The investigators had access to the data in the study and had final decision to submit for publication.

Approval for the RCSN was obtained from the Research Ethics Board at each participating institution. The current study was approved by the RCSN publications committee and the Sunnybrook Hospital Research Ethics Board.

Results

Demographics

Amongst 5027 consecutive patients admitted with an acute stroke, 4083 (81.2%) had an ischaemic and 939 (18.7%) had a hemorrhagic stroke. Mean age was 71 years, 48% were female. Twenty percent were younger than 60 and 32% older than 80. Seizures occurred in 138 (2.7%) patients (60 women and 78 men).

Clinical characteristics (Table 1)

Type of stroke

Intracranial hemorrhage was seen most frequently associated with patients experiencing seizures (39.1% vs. 18.1%, $P = 0.0001$). Amongst patients with seizures during hospitalization, 48.4% of patients had a partial anterior cerebral stroke, 21.9% had posterior circulation territory strokes, 17.2% had strokes involving the entire middle cerebral artery territory [total anterior cerebral stroke (TACS)], and 8.6% had LACS (Table 1).

Co-morbidities

Diabetes was seen in 17.4% of those patients with seizures versus 23.5% in those without seizures ($P = 0.09$). No differences in the scores for the Charlson-Deyo index were seen between these two groups ($P = 0.97$). Alcohol consumption was reported in 21 patients with seizures, compared with 733 without seizures (15.2% vs. 15.0%, $P = 0.24$).

Stroke severity-clinical presentation

Patients with seizures had more severe strokes in comparison to those without seizures (mean CNS ± (SD) score was 5.2 ± (0.3) for patients with seizures and 7.5 (±0.05) for patients without seizures; $P = 0.0001$). In terms of clinical presentation, patients with seizures were more likely to have neglect (32.8% vs. 18.7%, $P = 0.0001$) than their counterparts. No other differences were seen in the clinical presentation between patients with and without seizures (presence of weakness and dysphagia).

Seizures

Nineteen percent (26/138) of patients with seizures at the onset of stroke, had subsequent seizures, a higher percentage that in the group without seizures (96 of 4889 = 2%; $P = 0.0001$). Neither information regarding the type of seizures, nor the treatment used was available.

Outcome measures (Table 2)

Mean modified Rankin score at discharge for patients with and without seizures was 4.41 and 3.15 respectively ($P = 0.0001$). Only 90 (65%) of patients with seizures at stroke presentation remained alive upon discharge, compared with 4100 (84%) of those without seizures ($P = 0.0001$).

Stroke fatality at 30-days and 1-year was higher amongst those with seizures (36.2% vs. 16.8% for 30 day stroke-fatality and 49% vs. 28% for 1-year stroke – fatality, $P = 0.0001$).

Resource utilization

Only 16 patients who had seizures received thrombolytic therapy, whilst 589 without seizures received it (11.6% vs.12.1%, $P = 0.87$). A greater percentage of patients with seizures were admitted to the intensive care unit (21% vs. 9.9%, $P = 0.0001$), whilst patients without seizures were more frequently admitted to medical and neurological wards. Thirty-nine percent of patients without seizures and 29% of patients with seizures were admitted to stroke units ($P = 0.02$) (Table 2). Overall, the mean LOS of patients with seizures was 22.6 (±2.6)

Table 1 Characteristics of patients with seizures and stroke

Variables	Overall	Occurrence of seizures		
		Yes	No	*P*-value
No. patients	5027	138 (2.7%)	4889 (97.3%)	
Age (years)				
Mean	71.4 ± 0.2	68.6 ± 1.4	71.5 ± 0.2	0.02
Median	74	72	74	0.1
Age group				
< 60	983	36 (26.1%)	947 (19.4%)	0.1
60–79	2425	61 (44.2%)	2364 (48.4%)	
Older than 79	1619	41 (29.7%)	1578 (32.3%)	
Charlson index				
0	2002 (39.8%)	53 (38.4%)	1949 (39.9%)	0.9
1	1431 (28.5%)	39 (28.3%)	1392 (28.5%)	
2	768 (15.3%)	23 (16.7%)	745 (15.2%)	
3	826 (16.4%)	23 (16.7%)	803 (16.4%)	
Sex				
Female	2394	60 (43.5%)	2334 (47.7%)	0.3
Male	2633	78 (56.5%)	2555 (52.3%)	
Caucasian				
% of patients	55.5	61.6	55.3	0.14
Diabetes				
% of patients	23.3	17.4	23.5	0.09
CNS score				
Mean	7.41 ± 0.05	5.23 ± 0.31	7.47 ± 0.05	< 0.001
Median	8.5	5	8.5	< 0.001
NIH score				
Mean	9.74 ± 0.2	11.26 ± 1.1	9.67 ± 0.2	0.17
Median	8	11	8	0.11
Stroke type (% of patients)				
Hemorrhagic	18.7	39.1	18.1	< 0.001
Ischaemic	81.2	60.9	81.8	
Location of stroke (% of patients with ischaemic stroke)				
PACS	36.6	48.4	36.2	0.002
POCS	25.8	21.9	25.9	
LACS	17.6	8.6	17.8	
TACS	12.2	17.2	12.1	

PACS, partial anterior cerebral stroke; POCS, posterior circulation stroke; LACS, lacunar stroke; TACS, total anterior cerebral stroke.

days, whilst in the group without seizures was 16.3 (± 0.3) days ($P = 0.003$). No differences were seen in the use of speech therapy services and occupational and physical therapy services by the two groups in the in- and out-patient settings. Discharge to an acute care facility was seen in 22% of patients with seizures, whilst it was seen only in 8% of the ones without seizures ($P = 0.0001$).

Medical complications

Pneumonia and urinary tract infections were seen more frequent in patients with seizures ($P = 0.003$). (Table 2). Overall, similar results were observed when analyzing separately patients with ischaemic and hemorrhagic stroke (Table 3) or seizures at presentation (data not shown).

Multivariate analysis

In the univariate analysis, seizure at stroke onset, stroke severity, presence of pneumonia, development of a urinary tract infection, and prolonged hospital stay were associated to occurrence of seizures following stroke onset. After adjusting for confounders, stroke severity and hemorrhagic stroke, as well as low CNS score, presence of neglect, and seizures at stroke onset were associated with the occurrence of seizures after stroke. (Table 4).

Discussion

The presence of seizures after stroke constitutes a challenge for patients, families and clinicians. Limited information is available regarding the impact of seizures on the clinical outcome, resources utilization and disposition after stroke. In this large cohort study, we found that presence of seizures in patients with stroke was associated with higher stroke fatality, disability at discharge and prolonged LOS.

Our study confirms that stroke severity (a proxy of stroke size) is an important factor associated with the

Table 2 Outcome measures

Variables	Overall	Occurrence of seizures		*P*-value
		Yes n = 138 (%)	No n = 4889 (%)	
Admission to ICU	515 (10.3%)	29 (21.0%)	486 (9.9%)	0.0001
Admission to stroke unit	1941 (38.6%)	40 (29)	1901 (38.9)	0.0001
Disposition (alive patients only)				
Acute care facility	336 (8%)	20 (22.2)	316 (7.7)	0.0001
Home	1899 (45.3%)	18 (20.04)	1881 (45.8)	
Long-term care facility	519 (12.4%)	19 (21.1)	500 (12.2)	
Rehabilitation facility	1368 (32.6%)	29 (32.2)	1339 (32.6)	
Other	73 (1.7%)	< 5	69 (1.7)	
Length of hospital stay				
Mean (SD in days)	16.5 (0.3)	22.6 (2.6)	16.3 (0.3)	0.002
Disability at discharge				
Mean mRS (SD)	3.2 (0.03)	4.4 (0.1)	3.1 (0.03)	0.0001
Stroke fatality				
30-days	872 (17.3)	50 (36.2)	822 (16.8)	0.0001
1-year	1423 (28.3)	67 (48.6)	1356 (27.7)	0.0001

mRS, modified-Rankin scale.

Table 3 Outcome measures amongst patients with ischaemic and hemorrhagic stroke

Variables	Overall	Occurrence of seizures		*P*-value
		Yes n = 138 (%)	No n = 4882 (%)	
Ischemic stroke	4083 (81.2%)	84 (60.9)	3999 (81.8)	
Disposition (alive patients only)				
Acute care facility	203 (5.7%)	10 (18.5)	193 (5.5)	< 0.0001
Home	1695 (47.3%)	10 (18.5)	1685 (47.7)	
Long-term care facility	438 (12.2%)	13 (24.1)	425 (12)	
Rehabilitation facility	1193 (33.3%)	20 (37%)	1173 (33.2)	
Other	56 (1.6%)	Less than 5	55 (1.6%)	
Length of hospital stay				
Mean (SD in days)	16.4 (24.3)	20.6 (27.7)	16.3 (24.1)	0.11
Disability at discharge				
mRS ≤ 2	1583 (38.8)	9 (10.7)	1574 (39.4)	< 0.0001
Stroke fatality				
30 days	528 (12.9)	29 (34.5)	499 (12.5)	< 0.0001
1 year	977 (23.9)	40 (47.6)	937 (23.4)	< 0.0001
Hemorrhagic stroke	939 (18.7%)	54 (39.1)	885 (18.1)	
Disposition (alive patients only)				
Acute care facility	133 (21.8%)	10 (27.8)	123 (21.4)	0.15
Home	204 (33.4%)	8 (22.2)	196 (34.1)	
Long-term care facility	81 (13.3%)	6 (16.7)	75 (13.1)	
Rehabilitation facility	175 (28.7%)	9 (25)	166 (28.9)	
Other	17 (2.8%)	3 (8.3)	14 (2.4)	
Length of hospital stay				
Mean (SD in days)	16.8 (23.1%)	25.7 (33.5)	16.3 (22.2)	0.004
Disability at discharge				
mRS ≤ 2	194 (20.6%)	6 (11.1)	188 (21.1)	0.07
Stroke fatality				
30 days	344 (36.4%)	21 (38.9)	323 (36.3)	0.7
1 year	446 (47.2%)	27 (50)	419 (47.1)	0.7

mRS, modified-Rankin scale.

development of seizures. Early epileptiform activity has a deleterious effect on infarcted areas, perhaps by increasing the metabolic demand in a hypoxic tissue, causing a secondary brain damage. Cerebral blood flow, glucose and oxygen consumption increase substantially during generalized seizures to meet the tissue's enhanced requirements for energy [25–27]. Therefore it may be reasonably suggested that epileptic seizures worsen prognosis in stroke because epileptiform activity accelerates the cerebral glucose metabolism several fold and contributes to an increase in deleterious lactate levels. All seizures occurred either at onset or whilst in the hospital,

Table 4 Multivariate analysis: variables associated with the occurrence of seizures after stroke

	Occurrence of seizures	
Variable	OR (95% CI)	*P*-value
Presence of neglect	2.0 (1.3–3.1)	0.001
Seizure as part of stroke presentation	14.4 (8.2–25)	< 0.001
Hemorrhagic stroke (vs. ischaemic)	2.8 (1.7–4.5)	< 0.001
Low CNS score (mild strokes)	0.9 (0.9–1.0)	< 0.001

CNS, Canadian Neurological Scale; CI, confidence interval; OR, odds ratio.

a period during which there is still potentially salvable brain tissue, and this may determine a greater area of definite cerebral infarction, which in turn would be associated with a poorer clinical course [27]. This phenomenon could explain, at least in part, the higher utilization of resources, disability, mortality and LOS in patients with seizures.

Our study is in agreement with the frequency of seizures after stroke in previous studies ranging from 2 to 4% [27–36]. Similarly, previous studies have indicated a direct relationship between stroke size and seizures [34,35,37]. In our study, we used severity as a proxy of stroke size. In terms of localization of the stroke, patients with a partial or complete middle cerebral artery territory infarct were more commonly associated with seizures. This is an expected phenomenon as the middle cerebral artery largely covers the cerebral cortex and the most common arterial distribution for major strokes [27]. This is also most probably the explanation why neglect was seen more frequently in patients with seizures.

Interestingly, we found no association between seizures after stroke and age or comorbid conditions. These findings are in concordance with earlier studies [38–40]. We also found a lack of association between the use of health resources as speech, occupational, and physiotherapy in patients with stroke patients with and without seizures.

Our study has strengths and limitations that deserve to be mentioned. First, we have no long-term follow-up after discharge. Secondly, we do not have information on the results of EEG; some seizures could have been missed or some paroxysmal non-epileptic events could have been called seizures. Furthermore, continuous EEG when used in patients after ischaemic stroke or intracerebral hemorrhage have found that electrographic seizures are common after stroke and that most patients with electrographic seizures may not have clinical correlates; Thus, the incidence rate of seizure in the study. Thirdly, we have no information about history of epilepsy, types of seizures, the final management of seizures, and the use of antiepileptic drugs. Fourth, no detailed information on imaging was available. Finally, it is possible that unmeasured variables (e.g. race, ethnicity, co-morbidities not included in the study) could explain some of our findings. Fourth, despite the available information of the mechanism of stroke, there is no anatomical information (cortical or subcortical, insular vs. temporal involvement).

Despite these limitations, our study is the largest including comprehensive clinical-administrative data from Regional Stroke centers in Canada. Our study provides a robust and consistent association between the presence of seizures after stroke and higher disability, fatality rate, and length of hospital stay.

Practical implications for clinical management and discharge planning may arise from our study. The use of antiepileptic agents as a prophylactic treatment in patients with hemorrhagic strokes is a common practice in many centers worldwide, even though is not supported by strong, evidence-based clinical trials. Studies in that regard are needed. The strong impact of seizures on functional independence and quality of life, as well as in health resource utilization, reinforces the need for novel strategies to reduce the frequency of this complication. Our findings provide the first step in the understanding of factors in the development of seizures and epilepsy after stroke, and how these variables impact on stroke fatality, LOS and disability at discharge. Strategies targeting patients with seizures after stroke may be implemented to optimize access to specialized care, improve the prognosis and quality of care in these individuals.

Disclosure

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The project was reviewed and approved by the Publications Committee of The Registry of the Canadian Stroke Network. [Correction added on 17 November 2009, after first online publication: the text in the Disclosure section was amended.]

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