Early seizures in patients with acute stroke: Frequency, predictive factors, and effect on clinical outcome

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Background: Early seizure (ES) may complicate the clinical course of patients with acute stroke. The aim of this study was to assess the rate of and the predictive factors for ES as well the effects of ES on the clinical outcome at hospital discharge in patients with first-ever stroke.

Patients and methods: A total of 638 consecutive patients with first-ever stroke (543 ischemic, 95 hemorrhagic), admitted to our Stroke Unit, were included in this prospective study. ES were defined as seizures occurring within 7 days from acute stroke. Patients with history of epilepsy were excluded.

Results: Thirty-one patients (4.8%) had ES. Seizures were significantly more common in patients with cortical involvement, severe and large stroke, and in patient with cortical hemorrhagic transformation of ischemic stroke. ES was not associated with an increase in adverse outcome (mortality and disability). After multivariate analysis, hemorrhagic transformation resulted as an independent predictive factor for ES (OR = 6.5; 95% CI: 1.95–22.61; p = 0.003).

Conclusion: ES occur in about 5% of patients with acute stroke. In these patients hemorrhagic transformation is a predictive factor for ES. ES does not seem to be associated with an adverse outcome at hospital discharge after acute stroke.

Keywords: seizures, stroke, cortical involvement, hemorrhagic transformation

Introduction

Complications occurring during the early phase after an acute stroke are major determinants of the final outcome of this serious vascular event (Davenport et al 1996). Understanding the nature and timing of these complications is crucial for an appropriate management of patients with acute stroke.

Stroke is the most common cause of acute symptomatic seizures in the elderly population (Forsgren et al 1996). Although, there are different timing-based definitions of stroke-associated ES, most authors identify early seizures as those occurring within 7–14 days after acute stroke onset (Bladin et al 2000; Labovitz et al 2001; Lamy et al 2003; Ferro and Pinto 2004). Seizures occurring after this time window are defined as late seizures. This distinction underlies possible differences concerning the pathophysiology of and risk factors for early and late seizures.

Symptomatic seizures have been reported to occur in 2 to 33% of patients with acute stroke (Gupta et al 1988; Kilpatrick et al 1992; Giroud et al 1994; Ryvlin et al 2006). The reported wide range of percentages is probably explained by the analysis of retrospective studies, different window for defining ES (range 1–30 days) and the inclusion in the analysis of patients with different types of stroke. Several studies have tried to identify the predictive factors for ES after acute ischemic and hemorrhagic stroke with controversial results. Stroke severity, hemorrhagic stroke, and cortical involvement were the predictive factors more often reported (So et al 1996; Arboix et al 1997; Reith et al 1997; Bladin et al 2000; Labovitz et al 2001; Lamy et al 2003).

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The aim of this study was to determine the rate of and the predictive factors for ES as well as the influence of ES on the clinical outcome in patients with first-ever acute stroke.

Patients and methods

Patients with acute ischemic or hemorrhagic first-ever stroke admitted to the Stroke Unit at the Department of Cardiovascular Medicine, University of Perugia, from October 2004 to May 2007 were prospectively and consecutively included in this study. Patients with transient ischemic attack (TIA), subarachnoid hemorrhage, and cerebral vein thrombosis were excluded from the study as were patients with a history of epilepsy. All patients were assessed by the study neurologist to confirm the diagnosis and the aetiological subtypes of stroke (Adams et al 1993). Stroke was defined according to the World Health Organization's criteria, that is, sudden onset of signs of focal or global disturbance of cerebral function lasting more than 24 hours with no apparent nonvascular cause (WHO 1989). All patients underwent brain computed tomography (CT) scan on admission, which was repeated 3–7 days from stroke onset. Cerebral magnetic resonance imaging (MRI) was performed on selected patients (eg, in those with a second negative CT scan (10%)). Overall, 15% of patients were studied by MRI with diffusion weighted imaging. Ischemic stroke was classified as cortical and subcortical based on neuroimaging. The size of ischemic infarcts was classified as small if lesion $<$1.5 cm; medium if lesion was in a cortical superficial branch of middle cerebral artery (MCA), or lesion involving the MCA deep branch, or lesion internal border zone territories, or lesion in a cortical superficial branch of posterior cerebral artery (PCA), or lesion involving the PCA branch or lesion in a cortical superficial branch of anterior cerebral artery (ACA); large if the lesion involving whole territory of ACM, ACP or ACA, or the lesion involving two cortical superficial branches of MCA, or the lesion involving a cortical superficial branch of MCA associated to the MCA deep branch, or the lesion involving more than 1 artery territory and lesion involving brainstem or cerebellum $>$1.5 cm. In patients with hemorrhagic stroke the size was considered large if the maximal diameter of the lesion was $>$3 cm. Clinical outcome measured including mortality and disability at discharge, according to modified Rankin score: 0,1,2: non-disabling stroke; 3,4,5 : disabling stroke (De Haan et al 1995).

ES was defined as seizure occurring within 7 days from stroke onset, according to the International League Against Epilepsy guidelines (1993). Transient change in the level of consciousness or amnesia were not considered for a diagnosis of epileptic seizure.

Data on patient vascular risk factors were collected which included: age, gender, hypertension (blood pressure $>$140/90 at least twice before stroke under treatment with antihypertensive drugs), diabetes mellitus (glucose levels $>$126 mg dL preprandial on two examinations, glucose level $>$200 mg dL postprandial, or HbA1c $>$8.5%), current cigarette smoking, hyperlipidemia (cholesterol concentration of $>$200 mg dL and /or triglyceride concentration $>$140 mg dL on admission or already under statins), history of ischemic heart disease, atrial fibrillation, intermittent claudication, or previous transient ischemic attacks.

Four hundred and thirty-six consecutive patients enrolled over the final 18 months of the study were also examined for stroke severity on admission and the occurrence presence of hemorrhagic transformation (HT). Stroke severity was evaluated at admission using the National Institute of Health Stroke Scale (NIHSS). HT, defined as any degree of hyperdensity within the area of low attenuation, was evaluated in patients with ischemic stroke on admission by TC which was repeated 7 days later. In these patients the association between HT and antithrombotic therapy was also examined.

ES predictors were assessed by univariate analysis and multiple logistic regression analysis. In the univariate analysis, comparing each of the categorical baseline variables in patients with ES with those in patients without ES, χ^2-test or Fisher's exact test were used when appropriate. Statistical significance was set at $p < 0.05$. For the multiple logistic regression analysis, the independent variables were selected from the univariate analysis using backward stepwise analysis with a level of 0.1 as a screening criterion for selection of candidate variables.

The next step of analysis was aimed at identifying predictors of severe outcome. In the univariate analysis each of the baseline variables including ES of the group of patients alive/non disabled was compared to that group of patients dead/disabled using χ^2 test or Fisher's exact test when appropriate. Statistical significance was set at $<$0.05. Multiple logistic regression analysis was used to identify independent predictors of adverse outcome.

All analyses were performed with the SPSS/PC Win package 13.0 (SPSS Inc., Chicago, IL, USA).

Results

A total of 638 patients (mean age 72.8 ± 13.2 years) with a first-ever acute stroke were included in the study. Of them, 543 suffered an ischemic stroke (85.1%) and 95 had a hemorrhagic stroke (14.9%). ES were diagnosed in 31 patients (4.8%). Twenty-one of the patients with ES (67%) were

males. The clinical features of patients with and without seizure are reported in Table 1. No statistically significant difference concerning age, gender and risk factors for stroke were seen between patients with and without seizures. No difference was found in the rate of ES between ischemic and hemorrhagic strokes. In the univariate analysis cortical involvement was more frequent in patients with ES than in patients without ES (58% vs 33%). Furthermore, stroke lesion was larger in patients with ES than in patients without ES (29% vs 15%).

Globally, 436 consecutive patients (mean age: 72.8 ± 13.0; 368 ischemic stroke) were evaluated for stroke severity on admission and the presence of HT. In these patients, the univariate analysis showed that the initial stroke severity on admission was significantly higher in patients with ES than in patients without ES (means NIHSS: 13.2 ± 9.3 vs 10.0 ± 7.3; p = 0.05). HT was more common in patients with ES than in patients without ES (36.8% vs 7.7%; p = 0.001) (Table 2). In the patient group with ES, HT was cortical in 83.7% of the cases (6/7). After multivariate analysis, HT (OR = 6.58; 95% CI: 1.95–22.61; p = 0.003) resulted as an independent factor for developing seizures in patient with first ever stroke, while the NIHSS (OR: 1.47; 95% CI: 1.34–1.61; p = 0.001) and HT (OR: 8.45; 95% CI: 1.73–41.20; p = 0.008) were independently associated with adverse outcome. 41 patients had been taking anticoagulant and 161 patients had antiplatelet therapy before stroke onset. HT occurred in 6/41 (14.6%) and 15/161 (9.3%). No relation was observed between antithrombotic therapy and HT (p = 0.1 and p = 0.3 respectively).

At discharge, 348 patients were dead (66, 10.3%) or disabled (282, 44.2%) (Table 3). ES did not influence hospital mortality/disability (OR: 0.92; 95% CI: 0.31–2.73). Hemorrhagic stroke (OR: 7.24; 95% CI: 2.3–21.9; p = 0.001) and large lesion size (OR: 19.47; 95% CI: 5.86–6.46; p = 0.001) resulted being the most important predictive factors for disability.

Discussion

In this study, ES occurred in 4.8% of patients with ischemic or hemorrhagic stroke. The main findings of this study were that ES were more common in patients with cortical lesion than in those without cortical involvement and that ES were not associated with an adverse outcome at hospital discharge.

The reported rate of ES in our study was within the range (2% to 6%) of those reported in prospective studies in which ES were defined as those occurring within 7 days from of acute stroke onset (So El et al 1996; Labovitz et al 2001; Lamy et al 2003). No differences between age and gender were found between patients with and without ES. These data are consistent with those reported in previous studies (Reith et al 1997; Labovitz et al 2001), although age younger than 65 years and male gender have been shown to

Table 1 Main features of patients with and without ES

	Total n (%)	With ES n (%)	Without ES n (%)	Univariate analysis p
No. of patients	638	31(4.8)	607	
Mean age	72.8 ± 13.2	76.8 ± 10.3	72.6 ± 13.3	
Sex, male	364 (57)	21 (67)	343 (56.5)	
Risk factors				
Hypertension	450 (70.6)	26 (83.8)	424 (69.9)	
Diabetes	138 (21.6)	6 (19.3)	132 (21.2)	
Ischemic heart disease	112 (7.5)	6 (19.3)	106 (17.4)	
Atrial fibrillation	139 (21.8)	5 (16.1)	134 (22.2)	
Peripheral arterial disease	27 (4.2)	2 (6.4)	25 (4.1)	
Hyperlipidemia	240 (37.6)	11 (35.4)	229 (37.7)	
Smoking	155 (24.2)	10 (31.2)	145 (23.9)	
Previous TIA	30 (4.7)	1 (3.2)	29 (4.7)	
Clinical data				
Hemorrhagic stroke	95 (14.9)	5 (16.3)	90 (14.8)	
Lacunar	128 (20.0)	4 (12.9)	124 (20.5)	
Atherothrombotic	144 (22.5)	9 (29.0)	135 (22.2)	
Cardioembolic	150 (23.5)	7 (22.5)	143 (23.5)	
Cortical involvement	230 (36.0)	18 (58.1)	212 (33.2)	0.01
Large size	97 (15.2)	9 (29.0)	88 (14.8)	0.03

Table 2 Comparison of patients with and without ES evaluated for NIHSS and HT

	Total n (%)	With ES n (%)	Without ES n (%)	Univariate analysis
				p
No. of patients	436	22 (5.0)	414	
Mean age	72.8 ± 13.0	75.9 ± 11.4	72.6 ± 13.1	
Sex, male	251 (57.5)	16 (72.7)	235 (56.8)	
Risk factors				
Hypertension	321 (73.6)	19 (86.4)	302 (72.9)	
Diabetes	95 (21.8)	6 (27.2)	89 (21.5)	
Ischemic heart disease	57 (13.1)	2 (9.1)	55 (13.3)	
Atrial fibrillation	105 (24.1)	4 (18.1)	101 (24.3)	
Peripheral arterial disease	16 (3.7)	2 (9.1)	14 (3.4)	
Hyperlipidemia	171 (39.2)	10 (45.4)	161 (38.9)	
Smoking	129 (29.6)	10 (45.4)	119 (28.7)	
Previous TIA	22 (5.0)	1 (4.5)	21 (5.1)	
Clinical data				
Ischemic stroke	368 (84.4)	19 (86.3)	349 (84.2)	
Lacunar	100 (22.9)	4 (18.1)	96 (23.1)	
Atherothrombotic	95 (21.8)	7 (31.8)	88 (21.2)	
Cardioembolic	105 (24.1)	4 (18.1)	101 (24.4)	
Cortical involvement	168 (38.5)	14 (63.6)	154 (37.1)	0.01
Large size	65 (14.9)	6 (27.3)	59 (14.2)	0.008
Hemorrhagic transformation	34 (9.2)	7 (36.8)	27 (7.7)	0.001
NIHSS (score)	10.1 ± 7.5	13.2 ± 9.3	10.0 ± 7.3	0.05

Table 3 Patient characteristics and outcome

	Total n (%)	Rankin <3 n (%)	Rankin ≥3 n (%)	Univariate analysis
				p
No. of patients	638	290	348	
Mean age	72.8 ± 13.2	67.8 ± 13.1	76.9 ± 11.5	0.001
Sex, male	363 (56.9)	190 (65.5)	173 (49.7)	0.001
Risk factors				
Hypertension	450 (70.5)	192 (66.2)	258 (74.1)	0.04
Diabetes	136 (21.3)	60 (20.6)	76 (21.8)	
Ischemic heart disease	110 (17.2)	48 (16.5)	62 (17.8)	
Atrial fibrillation	138 (22.0)	39 (13.7)	99 (28.9)	0.001
Peripheral arterial disease	25 (3.9)	8 (2.7)	17 (4.9)	
Hyperlipidemia	244 (38.2)	122 (42.0)	122 (35.0)	0.057
Smoking	155 (24.2)	78 (26.8)	77 (22.1)	
Previous TIA	30 (4.7)	12 (4.1)	18 (5.2)	
Clinical data				
With ES	31 (4.8)	13 (4.5)	18 (5.2)	
Hemorrhagic stroke	95 (14.9)	25 (26.3)	70 (73.7)	0.001
Lacunar	133 (20.8)	72 (24.8)	61 (17.5)	0.03
Atherothrombotic	149 (23.3)	66 (22.7)	83 (23.8)	
Cardioembolic	152 (23.8)	46 (15.9)	106 (30.4)	0.001
Cortical involvement	242 (37.9)	83 (28.6)	159 (45.6)	0.001
Large size	106 (16.6)	15 (5.2)	91 (26.1)	0.001
NIHSS (score)	436/638	5.0 ± 3.3	14.2 ± 7.3	0.0001
Hemorrhagic transformation	34 (9.2)	5 (2.9)	29 (14.9)	0.0001

be a risk factors for ES in some other reports (Olsen et al 1987; Misirli et al 2006).

Consistently with the most recent studies (Labovitz et al 2001; Lamy et al 2003), hypertension, diabetes mellitus, smoking, hyperlipidemia, ischemic heart disease, atrial fibrillation or previous TIA were not associated with ES.

We did not find a significant correlation between seizure and hemorrhagic stroke such as providing negative data to the controversial debate related the increased rate of ES in patients with hemorrhagic stroke (Lo et al 1994; Arboix et al 1997; Reith et al 1997; Berges et al 2000; Bladin et al 2000; Labovitz et al 2001). We did not observe an association between stroke etiology, particularly cardioembolic stroke, and the occurrence of ES. This is of interest as cardioembolic infarction has been a controversial risk factor for ES for years (Lesser et al 1985; Kittner et al 1990; Giroud et al 1994; Kraus et al 1998; Bladin et al 2000; Misirli et al 2006; So et al 2006).

Our study showed that ES was significantly more frequent in stroke patients with cortical lesions than in those patients without cortical involvement such confirming the results of most previous studies (Kilpaptrik et al 1992; Lo et al 1994; Arboix et al 1997; Labovitz et al 2001; Lamy et al 2003), but not the results of some others (Gupta et al 1988; Shinton et al 1988). Early seizures after stroke onset are probably the clinical mirror of cortical brain damage. Cortical irritation can increase the excitability and lead to the onset of seizure.

The clinical relevance of the cortical involvement in the development of ES has been confirmed by a prospective study based on EEG in acute stroke patients. This study found a relationship between electrical epileptic activity and cortical lesion (Carrera et al 2006). In our study, after multivariate analysis, the cortical involvement was not significant for ES (OR: 2.54; 95% CI: 0.85–7.55; $p = 0.09$), although a trend was observed.

Lesion size (Gupta et al 1988), and especially stroke severity, were reported to be related to ES. The prospective Copenhagen study (Reith et al 1997) of ischemic stroke patients showed that initial stroke severity measured with the Scandinavian Stroke Scale was the only factor related to ES, and initial stroke severity assessed by NIHSS at admission, was found to be an independent predictor of electrical epileptic activity (Carrera et al 2006). Another prospective multicenter study reported that stroke severity was independently associated with seizure after acute ischemic stroke (Bladin et al 2000), while another study did not confirm these data (Labovitz et al 2001). Also our data demonstrated that large size of infarct and initial stroke severity were related to the development of ES. However, after the multivariate analysis these factors did not result statistically significant.

We identified hemorrhagic transformation as a risk factor for ES in first-ever stroke patients. In all patients except one, the HT was cortical. The pathophysiology of seizures after stroke is not completely understood but several mechanisms are hypothesized: cellular biochemical dysfunction with membrane instability of injured cells; transient excitoxic neurotransmitter release, such as glutamate, secondary to hypoxia; free radical damage; alteration of energy metabolism; transient depolarizations of the ischemic penumbra with a resulting electrical irritable tissue (Heuts-van Raak et al 1996; Herman 2002; Camilo and Goldstein 2004). The presence of HT, especially in cortical regions, where it is often associated with edema, could increase the excitability of the cortical ischemic penumbra tissue, which is already suffering. Being so, cortical HT could be hypothesized as a focus for seizure activity. The increased brain excitability in the presence of HT seems to be confirmed by a recent study that has evidenced HT as an independent predictor of epilepticus status in acute ischemic stroke (Bateman et al 2007).

We did not find an association between HT and antithrombotic therapy during acute stroke, being so, we hypothesized that the use of anticoagulant or antiaggregants is not relevant for the presence of ES.

The influence of post-stroke ES on functional outcome is controversial. In the present study, ES were not associated with an adverse outcome at discharge. However some studies have reported a higher disability/mortality in patients with post-stroke ES (Bladin et al 2000; Lamy et al 2003). In particular, in a prospective study the in-hospitality mortality rate was significantly higher in ischemic stroke patients with ES than in those without ES (Arboix et al 2003). This association has not yet been confirmed by other studies after adjusting for stroke severity (Reith et al 1997; Labovitz et al 2001). Some authors have hypothesized that ES in ischemic stroke patients could worsen the patient outcome, because it causes additional metabolic stress in the suffering penumbral area (Reith et al 1997; Camilo and Goldstein 2004). However, there are no data available that ischemic damage could be increased by the hyperexcitability and the electric activity of cell membranes in necrotic tissue.

In conclusion, the result of our study show that about 5% of patients with acute stroke developed ES within 7 days from stroke onset and that cortical hemorrhagic transformation of ischemic stroke is a risk factor for ES. Finally, ES does not seem to be an independent predictor for adverse outcome.

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