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ORIGINAL COMMUNICATION

Acute seizures in acute ischemic stroke: does thrombolysis have a role to play?

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Abstract Seizures appear at stroke presentation, during the acute phase or as a late complication of stroke. Thrombolysis has not been investigated as a risk factor despite its potential neurotoxic effect. We try to identify risk factors for seizures during the acute phase of ischemic stroke in a cohort including thrombolysed patients. We undertook a case–control study at a single stroke center using data from Acute Stroke Registry and Analyse of Lausanne (ASTRAL). Patients with seizure occurring during the first 7 days following stroke were retrospectively identified. Bi-variable and multivariable statistical analyses were applied to compare cases and randomly selected controls. We identified 28 patients experiencing from seizures in 2,327 acute ischemic strokes (1.2 %). All seizures occurred during the first 72 h. Cortical involvement, thrombolysis with rt-PA, arterial recanalization, and higher initial NIHSS were statistically associated with seizures in univariated analysis. Backward linear regression identified cortical involvement (OR 7.53, 95 % CI 1.6–35.2, $p < 0.01$) and thrombolysis (OR 4.6, 95 % CI 1.6–13.4, $p = 0.01$) as being independently associated with seizure occurrence. Overall, 3-month outcome measured by the modified Rankin scale (mRS) was comparable in both groups. In the subgroup of thrombolysed patients, outcome was significantly worse at 3 months in the seizure group with 9/12 (75 %) patients with mRS $\geq$3, compared to 6/18 (33.3 %) in the seizure-free group ($p = 0.03$). Acute seizures in acute ischemic stroke were relatively infrequent. Cortical involvement and thrombolysis with rt-PA are the principal risk factors. Seizures have a potential negative influence on clinical outcome in thrombolysed patients.

Keywords Thrombolysis · rt-PA · Neurotoxicity · Epileptogenesis

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Introduction

Stroke patients may experience epileptic seizures at stroke presentation, in the acute phase (commonly defined as the first 7 days) or as a late complication [1]. The incidence of post-stroke seizures varies between studies: 8.9 % of patients suffering from ischemic or hemorrhagic stroke developed post-stroke epilepsy after 9 months of follow-up [2] and 3.2 % after 7 years in another survey [3]. Reported seizure incidence during the acute phase of stroke was 6.3 % during the first 24 h in a mixed stroke population [4] and 14 % during the first week after a hemorrhagic event [5]. Younger age [6], male gender [7], cortical involvement, and a hemorrhagic component have consistently been found to be seizure predictors [7]. Thrombolysis has, to our knowledge, not been investigated as a risk factor for early seizures, despite its potential neurotoxic [8] and possible epileptogenic [9, 10] effects in animals.

The aim of our study was to identify risk factors for seizures during the acute phase of ischemic stroke in a

large consecutive series of patients that included thrombolysed patients.

Methods

We undertook a case–control study at our tertiary care center. We used data from the Acute Stroke Registry and Analyse of Lausanne (ASTRAL) [11] containing all acute ischemic stroke arriving within 24 h after last proof of good health at our center. Of note, all patients undergo continuous monitoring in our stroke unit for at least 24 h and for a median of 54 h and are then transferred to a standard hospital bed in the stroke unit. Demographics, stroke characteristics, laboratory and imaging data (acute perfusion CT in most patients, and subacute head CT or MRI in most patients) and clinical outcome data are collected prospectively. Patients whose main diagnosis was transient ischemic attack, primary hemorrhagic stroke and cerebral venous thrombosis were excluded. The scientific use of the ASTRAL data was approved by the ethics commission for research on humans of the Canton of Vaud, subcommission III.

In ASTRAL, we retrospectively identified all patients with a seizure according to IALE and IBE definition [12] during the first 7 days following stroke, including first ever seizures or recurrent ones, by searching within the registry and by linking the ASTRAL patients to our EEG reports from January 1, 2004 until September 31, 2011 (93 months). The EEG reports are standardized and include the reason for the study, detailed clinical and circumstantial description, and antiepileptic medications used at the time of the exam.

As controls, we randomly selected 100 patients from ASTRAL without acute seizures during the same time period. Matching was not performed in order to avoid arbitrary exclusion of possible precipitating factors. The randomization was done using an Excel table, adding an additional variable with the (= RAND) function. Patients were ranked according to this new variable. The first hundred patients were selected.

For each patient, time of seizure's occurrence, type of seizure according to the ILAE classification [13], and concomitant anti-epileptic treatment were recorded by reviewing the according medical files.

For case and control patients, all data concerning the stroke were extracted from ASTRAL. In particular, presence of previous stroke, statin use, and alcohol abuse were assessed. Laboratory data included acute glucose, sodium (Na^+), and total cholesterol values. Acute stroke localization (involving the cortex or not), etiology according to the TOAST classification [14] plus dissection, NIHSS on admission, and use of iodine contrast for acute imagery were also assessed. Intravenous thrombolysis with recombinant tissue plasminogen activator (rt-PA) or acute endovascular treatments according to current guidelines [15, 16], the presence of arterial occlusion on initial arterial imaging (mostly CT angiography), partial or complete recanalization at 12–48-h follow-up imaging (CT or MR angiography or Doppler), and symptomatic hemorrhagic transformation according to the ECASS-II trial [17], and radiological hemorrhagic transformation according to the ECASS classification (when a control imagery was available) were also recorded. Finally, the modified Rankin scale (mRS) at 7 days and 3 months and mortality were obtained either during a follow-up visit at our stroke clinic or by phone by Rankin-certified medical personnel. Data not routinely registered in ASTRAL such as previous seizures, premorbid and post-stroke use of benzodiazepines and anti-epileptic drugs were obtained by reviewing all medical records.

Comparisons between the two groups were performed using two-tailed Fisher's exact, χ^2, Mantel–Haenszel χ^2, or *t* tests, as required. In order to adjust the results for possible confounders, the variables that were associated with seizure occurrence with a $p < 0.05$ in the univariate analysis were entered in a backward linear regression using acute seizure as dependant variable. Receiver operating characteristic (ROC) curves and area under the curves (AUC) were calculated for the different regression models. Patients who seized at stroke onset were excluded from bi-variate and multivariate analysis for factors associated with seizures' occurrence. Indeed in those patients, the outcome (seizure) precedes the exposition (potential thrombolysis). Analyses were performed with version 20 of SPSS (SPSS Inc., IBM).

Results

We identified 28 patients suffering from acute seizures in 2,327 consecutive acute ischemic strokes (1.2 %). All seizures occurred during the 72 h of stroke onset and mostly so within the first 24 h (Fig. 1). Eight (28.5 %) patients had seizure at stroke onset. Of these latter patients, only one received rt-PA (endovascular recanalization with intra-arterial use of rt-PA), based on persisting focal deficits and focal hypoperfusion on CT-perfusion). The seven other patients with seizures at stroke onset were not thrombolysed. Most seizures were primarily generalized, followed by focal seizures with impairment of consciousness (Fig. 2). Among the five patients with status epilepticus, one had simple partial, two had complex partial and two had generalized status epilepticus. Of note, seizure's type distribution was the same in thrombolysed patients and in the non-thrombolysed ones (Table 1).

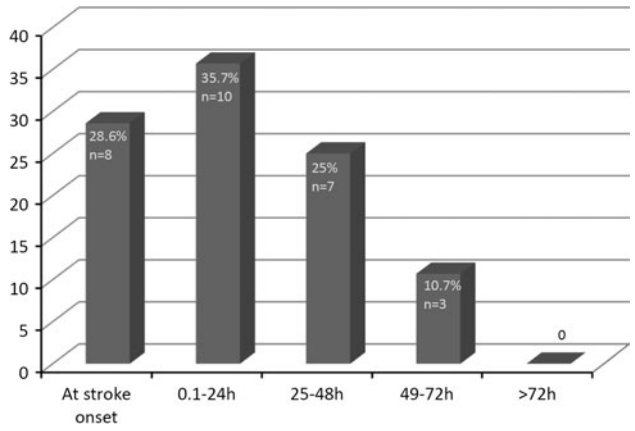

Fig. 1 Time of seizure occurrence within the first 7 days after acute ischemic stroke

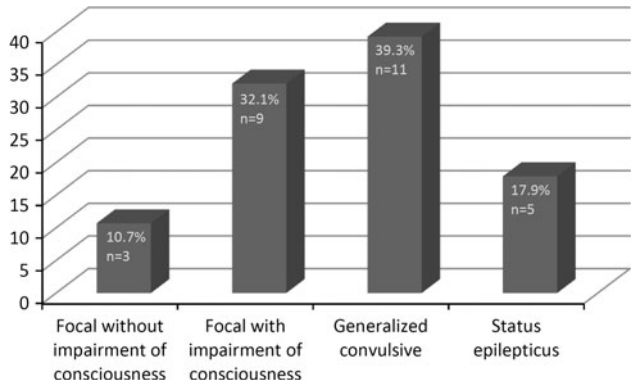

Fig. 2 Type of seizure according to the ILAE classification [12]

Demographics, stroke features, and clinical outcomes are shown in Table 2. Demographics were globally comparable. Also, there was no difference regarding premorbid treatment or for the presence of previous clinical stroke. Moreover, neither prevalence of previous seizures nor the premorbid use of anti-epileptic was different in both groups. Symptomatic and radiological hemorrhagic transformation occurred in comparable rates in both group. The admission metabolic values were also similar.

Several potential differences emerged in univariate analysis. Cortical involvement was significantly associated with seizures ($p < 0.01$), as was thrombolysis with rt-PA ($p < 0.01$). Seizure patients had a higher admission NIHSS ($p < 0.01$) and had higher rates of recanalization at follow-up imaging ($p < 0.01$). Regarding stroke etiology, there were no global differences, but lacunar infarcts were completely absent in the seizure group. Radiological hemorrhagic transformation occurred non-significantly more frequently in the control group. Uncertainty regarding the precise time of stroke onset was non-significantly more frequent in the control group.

Somewhat more patients in the seizure group tend to reach a poor functional outcome (mRS $\geq$3) at 3 months (Table 3). However, when analyzing the subgroup of thrombolysed patients only (Table 3), outcome was significantly worse at 3 months in the seizure group, but there was no difference at 7 days. Of note, in this subgroup analysis, the NIHSS was comparable with a median of 17.5 ($\pm$ 5.7) in seizure group versus 16.6 ($\pm$ 8.3) in the seizure-free one ($p = 0.56$, t test). The rate of symptomatic hemorrhagic transformation was also the same with one patient in each group.

Backward linear regression including cortical involvement, NIHSS on admission, recanalization thrombolysis identified cortical involvement (OR 7.53, 95 % CI 1.6–35.2, $p < 0.01$) and thrombolysis (OR 4.6, 95 % CI 1.6–13.4, $p = 0.01$) as being independently associated with seizure occurrence. The ROC curve for the different prediction models are shown in Fig. 3. Cortical involvement and thrombolysis is shown in Fig. 3a; the AUC is 0.7 (95 % CI 0.55.0–84). Figure 3b shows the ROC curve for cortical involvement with an AUC of 0.7 (95 % CI 0.57–0.81) and Fig. 3c for thrombolysis with a AUC of 0.69 (95 % CI 0.55–0.82).

Discussion

We found an incidence of 1.2 % of seizures within the first 7 days after ischemic stroke, which is lower than the previously reported 4.2 % of the ischemic subgroup reported by Beghi et al. [4], and clearly lower than electrical seizure patterns identified during continuous EEG monitoring in such patients reported by our group [18]. As opposed to

Table 1 Type of seizure according to acute stroke treatment

	Thrombolysed patients ($n = 12$)		Not thrombolysed patients ($n = 16$)		p value (test)
	n	%	n	%	
Focal without impairment of consciousness	2	16.7	1	6.3	0.61 (χ^2)
Focal with impairment of consciousness	3	25	6	37.5	
Generalized convulsive	4	33.3	7	43.7	
Status epilepticus	3	25	2	12.5	

Table 2 Comparison of seizure group (excluding patients with seizure at stroke onset) and control group

	Seizure group ($n = 20$)		Control group ($n = 100$)		p value (test)
	n, median (IQR) or mean (SD)	% or range	n, median (IQR) or mean (SD)	% or range	
Patient characteristics					
Age (median and IQR)	71 (17)	18–86	70.9 (18.5)	24–93	0.37 (t)
Male gender	10	50	59	59	0.45 (χ^2)
OH abuse	2	10	7	7	0.92 (Fisher)
Previous seizures	1	5	4	4	0.99 (Fisher)
Previous clinical stroke					
Ischemic	6	30	28	28	
Hemorrhagic	0	0	1	1	
None	14	70	71	71	0.89 (Fisher)
Pre-stroke treatment					
Statin	5	25	24	24	0.92 (χ^2)
Benzodiazepine	2	10	10	10	0.59 (Fisher)
Anti-epileptic drugs	1	5	4	4	0.99 (Fisher)
Admission metabolic values (mean and SD)					
Glucose value (mmol/l)	6.48 (1.0)	5.1–7.9	7.7[a] (2.8)	4–19	0.07 (t)
Na^+ (mmol/l)	140 (3.71)	129–145	141 (3.0)	131–140	0.67 (t)
Cholesterol (mmol/l)	5.1[b] (1.1)	3.4–7.6	5.51[c] (1.8)	2.6–15.8	0.31 (t)
Stroke characteristics and treatment					
Stroke localization					
Involving cortex	18	90	50	50	<0.01 (Fisher)
Stroke etiology					
Atherosclerosis (with ≥50 % stenosis)	4	20	20	20	
Cardiac	7	35	29	29	
Lacunar	0	0	14	14	
Arterial dissection	1	5	5	5	
Multiple/coexisting	1	5	7	7	
Unknown/rare	7	35	25	25	0.58 (χ^2)
Stroke onset					
Known	12	60	53	53	
Approximately known (± 1 h)	2	10	20	20	
During sleep	3	15	22	22	
Unknown but < 24 h	3	15	5	5	0.26 (χ^2)
NIHSS on admission (median and IQR)	14.8 (15)	1–32	9.35 (13)	0–33	<0.01 (t)
CT with contrast	14	70	81	81	0.26 (χ^2)
Thrombolysis with rt-PA	11	55	18	18	<0.01 (χ^2)
Complete or partial recanalization after documented occlusion	9	45	15	15	<0.01 (χ^2)
Symptomatic hemorrhagic transformation	1	5	6	6	0.99 (Fisher)
Radiologic hemorrhagic transformation when documented	7[d]	39	10[e]	19.3	0.094 (χ^2)

[a] 99 values/100

[b] 17 values/20

[c] 90 values/100

[d] 18 available/20

[e] 52 available/100

Table 3 Comparison of clinical outcome of seizure and control group

All patients	Seizure group ($n = 28$)		Control group ($n = 100$)		p value (test)
Clinical outcome					
mRS ≥3 at 7 days	17	60.7	48	48	0.23 (χ^2)
mRS ≥3 at 3 months	16	57.2	39	39	0.09 (χ^2)
Death at 3 months	6	21.4	18	18	0.68 (χ^2)
Thrombolysed patients only	**Seizure group ($n = 12$)**		**Control group ($n = 18$)**		**p value (test)**
Clinical outcome					
mRS ≥3 at 7 days	10	83.3	11	61.1	0.37 (Fisher)
mRS ≥3 at 3 months	9	75	6	33.3	0.02 (χ^2)
Death at 3 months	2	16.6	4	22.2	0.99 (Fisher)

previous studies in this field [2–5], we limited our analysis exclusively to ischemic stroke and in acute phase. The higher incidence in most previous studies focusing on acute seizure ranging from 1.2 to 6.3 % [4, 19–22] may partially be explained by the inclusion of intracerebral hemorrhages.

The other principal finding of our results is the association of acute seizures with thrombolysis with rt-PA. Indeed, patients receiving rt-PA have an OR for seizure occurrence of 4.6 after correction for the main confounding factors. This was not explained by symptomatic or radiological hemorrhagic transformation as a seizure trigger or sign of reperfusion injury. One hypothetical explanation may be recanalization with free-radical production and reperfusion injury that may trigger seizures, even in the absence of hemorrhage. A small series [23] described dramatic neurological recovery after seizures appearing during the thrombolysis with rt-PA. The authors argued that the seizures might be a sign of early recanalization and thus, of a good outcome [24]. However, in our study, recanalization was not associated with seizure occurrence in multivariate analysis.

A further and probably more likely explanation could be related to the rt-PA itself, which is known to be neurotoxic in vitro with a large amount of evidence recently reviewed [8]. Moreover, this molecule has also been implicated in epileptogenesis in an animal model [9, 25, 26]. This supports the probable role of rt-PA as of seizure facilitator in acute ischemic stroke, and could corroborate the advantage of thrombolytic agents without neurotoxic effect [27]. Moreover, it is interesting to note that seizures were not reported as side-effects in the randomized studies that established the efficacy of rt-PA for ischemic stroke [28–30].

Toxicity of iodine contrast did not play a role in seizure induction in our cohort: 70 % of patients with seizure received contrast and 81 % did in the control group ($p = 0.27$).

As previously known, cortical involvement seems to represent the strongest predictor of seizure occurrence [2, 4], this association also occurs with other brain pathologies such as trauma [31] and tumor [32]. In our view, this reflects the importance of the neocortex in seizure genesis [33].

Concerning stroke etiology and in contrast to previous studies [7, 34], our data do not suggest that cardiac sources represent an independent relevant factor. However, lacunar infarct was completely absent in the seizure group, reinforcing the role of cortical involvement in seizure genesis.

Higher total cholesterol level has been previously described to be "protective" from seizure [4, 19]. In this regard, neurosteroids, derived from cholesterol, are known to have anticonvulsant and antiepileptogenic activities [35]. Moreover, lower cholesterol levels are associated with greater risk for symptomatic hemorrhagic transformation after recanalization therapy for ischemic stroke [36]. Our data do not confirm the "protective" effect of hypercholesterolemia or prestroke statin use against acute seizure, perhaps because of its marginal effect and limited number of cases.

As discussed in a comprehensive review [1], seizure in the acute stroke setting probably do not influence short- and long-term outcome when corrected for confounding factors in patients without thrombolytic treatments. Our study shows a trend to a less favorable outcome for patients with seizures; this is possibly explained by the markedly higher median NIHSS on admission of these patients (14.8; IQR: 15 vs. 7; IQR: 13, $p < 0.01$) in the whole group. As seizure, in this setting, is a stroke manifestation, it appears logical that the outcome is mainly predicted by the brain damage itself. However, in the subgroup analysis of thrombolysed patients only, occurrence of seizure is associated with worse outcome at 3 months without any difference in NIHSS on admission nor in the symptomatic

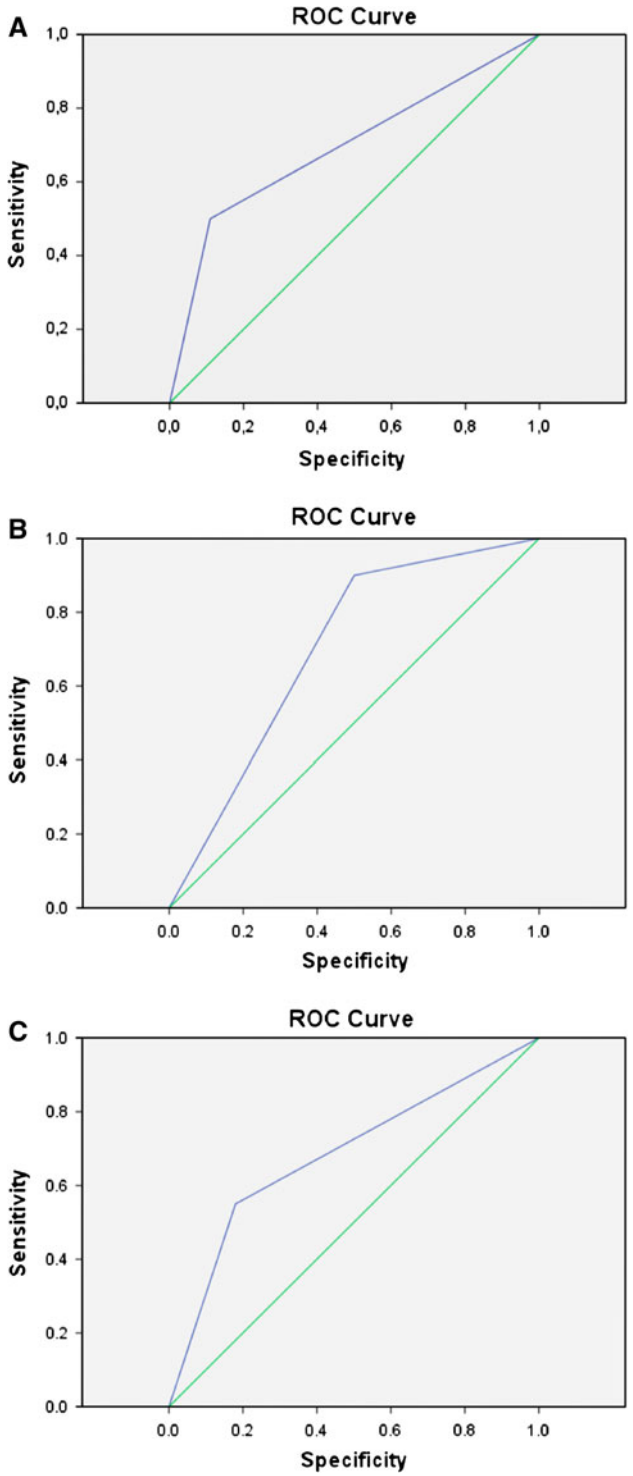

Fig. 3 ROC curves for the different variables included in the regression model. **a** For the model including "Cortical involvement" and "thrombolysis"; AUC: 0.7 (95 % CI 0.55–0.84). **b** For the variable "Cortical involvement"; AUC: 0.7 (95 % CI 0.57–0.81). **c** For the variable "Thrombolysis"; AUC: 0.69 (95 % CI 0.55–0.82)

hemorrhagic transformation rate. This is in line with a recent publication which showed that seizures within 24 h of stroke onset were associated with worse outcome in stroke patients undergoing endovascular thrombolysis with rt-PA [37]. This finding could have some possible direct implications. Indeed, as rt-PA is clearly associated with seizures and as their occurrence worsens the outcome in the thrombolysed patients, the use of another thrombolytic agent could be interesting.

Our results show that neither previous seizures nor the premorbid use of anti-epileptic drugs or alcohol abuse has any effect in seizure prediction.

The limitations of our study are its partially retrospective nature of cases' identification and data collection, which may lead to under-ascertainment; however, at our center, all stroke patients with a clinical suspicion of in- or out-of-hospital seizures undergo an EEG, including on weekends. Even if the seizure incidence was possibly underestimated, we believe that this did not influence the comparison of groups. The relatively low incidence may also be explained by our inclusion criteria (only acute setting and after ischemic stroke). The relatively low number of patients with seizures limited the power of the study to identify other, less important predictors. We also did not analyze the recurrence of seizure after the initial 7 days and therefore cannot say whether acute phase seizures after ischemic stroke predispose to further seizures later on. Finally, our study shows an association between thrombolysis and acute seizures, which do not mean causality.

In conclusion, acute seizure in ischemic stroke seems relatively infrequent, and the cortical involvement is the principal risk factor. Our results also show that thrombolysis with rt-PA may increase the likelihood of epileptic seizures in the acute phase of ischemic stroke, independently from recanalization or symptomatic intracerebral hemorrhage. The outcome seems negatively influenced by seizure occurrence in thrombolysed patients only. This supports (in our view) the use of non-epileptogenic thrombolytic agents. In the future, seizures in thrombolysed patients should be assessed prospectively in acute but also in delayed phase. Indeed, post-stroke epilepsy increases morbidity of stroke. If this association is confirmed in the chronic phase, "non-epileptogen" thrombolytic agent should be even more preferred.

Conflicts of interest Vincent Alvarez: nothing to disclose. Andrea O. Rossetti: research support: Pfizer, UCB, Sandoz, EISAI, and GSK. Patrik Michel: research support: Lundbeck Europe, consulting: Lundbeck Europe, Boehringer-Ingelheim, Bayer.

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