Unexplained Early Neurological Deterioration After Intravenous Thrombolysis
Incidence, Predictors, and Associated Factors

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Background and Purpose—Early neurological deterioration (END) after anterior circulation stroke is a serious clinical event strongly associated with poor outcome. Regarding specifically END occurring within 24 hours of intravenous recombinant tissue-type plasminogen activator, apart from definite causes such as symptomatic intracranial hemorrhage and malignant edema whose incidence, predictors, and clinical management are well established, little is known about END without clear mechanism (END unexplained).

Methods—We analyzed 309 consecutive patients thrombolysed intravenously ≤4.5 hours from onset of anterior circulation stroke. END unexplained was defined as a ≥4-point deterioration on 24-hour National Institutes of Health Stroke Scale, without definite mechanism on concomitant imaging. END unexplained and no-END patients were compared for pretreatment clinical and imaging (including magnetic resonance diffusion and diffusion/perfusion mismatch volumes) data and 24-hour post-treatment clinical (including blood pressure and glycemic changes) and imaging (24-hour recanalization) data, using univariate logistic regression. Exploratory multivariate analysis was also performed after variable reduction, with bootstrap analysis for internal validation.

Results—Among 33 END patients, 23 (7% of whole sample) had END unexplained. END unexplained was associated with poor 3-month outcome (P=0.01). In univariate analysis, admission predictors of END unexplained included no prior use of antiplatelets (P=0.02), lower National Institutes of Health Stroke Scale score (P<0.01), higher glycemia (P=0.03), larger mismatch volume (P=0.03), and proximal occlusion (P=0.01), with consistent results from the multivariate analysis. Among factors recorded during the first 24 hours, only no recanalization was associated with END unexplained in multivariate analysis (P=0.02).

Conclusions—END unexplained affected 7% of patients and accounted for most cases of END. Several predictors and associated factors were identified, with important implications regarding underlying mechanisms and potential prevention of this ominous event. (Stroke. 2014;45:2004-2009.)

Key Words: stroke ■ thrombolytic therapy

After intravenous recombinant tissue-type plasminogen activator (IV-rtPA) for acute ischemic stroke (AIS), clinical evolution in the first 24 hours is largely unpredictable, underlying the need to better investigate this time window. Although the majority of patients with AIS substantially improve after IV-rtPA, a fraction experience early neurological deterioration (END). Because END consistently predicts poor outcome, it is important to prevent or treat this detrimental event. However, many uncertainties still preclude its informed management. First, estimates of its incidence vary greatly, underlying the need to better investigate this time window. Although the majority of patients with AIS substantially improve after IV-rtPA, a fraction experience early neurological deterioration (END). Because END consistently predicts poor outcome, it is important to prevent or treat this detrimental event. However, many uncertainties still preclude its informed management. First, estimates of its incidence vary greatly, underlying the need to better investigate this time window.

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no specific action is usually taken to revert the clinical deficit and hence prevent poor outcomes. However, although hemodynamic and metabolic factors are suspected as underlying mechanisms, this has not been directly examined to date. To date, unexplained END has been only addressed in nonthrombolysed AIS, which may not generalize to the IV-tPA setting. Thus, the incidence, predictors, and associated factors of post-thrombolysis END, are still largely unknown and are the topic of the present work.

Methods

Patients
We extracted all consecutive patients who received IV-tPA within 4.5 hours of stroke onset between January 2003 and March 2013 from our prospective database, increased to 4.5 hours from 2008. Patients who underwent endovascular therapy were excluded given that in this setting the END may be directly related to the procedure. We then selected patients with middle cerebral artery (MCA) stroke because it is the most common subtype and its pathophysiology is well known. Decision to treat by IV-tPA was made by stroke neurologists according to current European guidelines, except that age >80 years was not a contraindication. Relevant clinical data were extracted from the database (see online-only Data Supplement). Stroke severity was assessed using the National Institutes of Health Stroke Scale (NIHSS) before and at 1 and 24 hours after treatment. Poor outcome was defined as 3-month modified Rankin Scale score ≥2.

In accordance with French legislation, Institutional or Ethics Committee approval was not required for this study because it only implied retrospective analysis of anonymized data collected as part of routine clinical care. Likewise, written consent was not necessary for IV-tPA, which is part of routine care.

Imaging Protocol

MRI is systematically implemented as first-line pretreatment work-up in patients for thrombolysis in our center. The admission protocol, performed on a 1.5-T scanner (Signa EchoSpeed, GE Healthcare), included fluid-attenuated inversion recovery, diffusion-weighted imaging (DWI), T2*-weighted gradient echo imaging, intracranial 3-dimensional time-of-flight magnetic resonance angiography, and perfusion-weighted imaging (PWI) whenever feasible. The DWI–PWI patterns and hypoperfusion or DWI lesion volumes were not the basis for clinical decision making except when there was uncertainty of potential for benefit. Patients in whom MRI was contraindicated underwent computed tomography (CT) and, whenever feasible, CT angiography; CT perfusion was performed only occasionally. A follow-up imaging (MRI, or CT if contraindicated) was scheduled within 24 hours after treatment and included the same set of sequences as the admission MRI save for PWI. Additional magnetic resonance or CT was also obtained in these settings setting the END may be directly related to the procedure. We then selected patients with middle cerebral artery (MCA) stroke because it is the most common subtype and its pathophysiology is well known. Decision to treat by IV-tPA was made by stroke neurologists according to current European guidelines, except that age >80 years was not a contraindication. Relevant clinical data were extracted from the database (see online-only Data Supplement). Stroke severity was assessed using the National Institutes of Health Stroke Scale (NIHSS) before and at 1 and 24 hours after treatment. Poor outcome was defined as 3-month modified Rankin Scale score ≥2.

In accordance with French legislation, Institutional or Ethics Committee approval was not required for this study because it only implied retrospective analysis of anonymized data collected as part of routine clinical care. Likewise, written consent was not necessary for IV-tPA, which is part of routine care.

Unexplained END

END was defined as an NIHSS score increase (ΔNIHSS) of ≥4 points between baseline and 24 hours, as used in previous studies on post-tPA END. The first 24 hours is the critical period for both favorable and unfavorable evolution, the special case of malignant edema apart. The medical and radiological records of each END case were reviewed by a stroke physician (P.S.) and a neuroradiologist (M.T.) and adjudicated in consensus for potential cause, taking into account the sudden or progressive onset of the deterioration, the neurological function that worsened, and the findings on imaging performed at the time of deterioration. sICH was identified according to the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST) criteria, defined as parenchymal hemorrhage type 2 based on European Cooperative Acute Stroke Study (ECASS) imaging classification on the imaging obtained at time of worsening and a NIHSS ≥4 deterioration. Early malignant edema was considered if brain swelling and midline shift were present together with worsening of consciousness. Early recurrent ischemic stroke was defined as the occurrence of new neurological symptoms suggesting the involvement of initially unaffected vascular territories and evidence of corresponding ischemic lesions on follow-up imaging, which excludes arterial reocclusion, proximal extension, or distal embolism of the original thrombus. Thus, END was operationally defined as END without evidence for any of the above causes or other potentially causative definite medical complication (eg, poststroke seizure).

Statistical Analysis

Continuous variables with a normal distribution were described as mean±SD and non-normally distributed variables as median and interquartile range. END patients with a cause were excluded from further analysis. Associations between END and pre- or post-treatment variables were assessed as odds ratios (ORs) and 95% confidence intervals (95% CIs) in univariate logistic models with END as the dependent variable. Pre- and post-treatment variables associated with END in univariate analysis at a level of P<0.20 were candidates for inclusion into a multivariate logistic regression model for 10 events of the dependent variable. Therefore, considering the relatively small number of END in this sample (see Results), we used oblique principal component cluster analysis for variable reduction. Exploratory multivariate logistic regression was then used with the remaining variables, using a Firth correction, which is less prone to overfitting. We then performed an internal validation of each final logistic model (pre- and post-treatment models), based on 1000 bootstrap replicates. Statistical analyses were performed using SAS 9.3 (SAS Institute, Inc, Cary, NC) and SPSS 16.0 (SPSS Inc).

Results

Study Population

During the study period, 119 consecutive patients (81 with MCA stroke) underwent endovascular procedures and were excluded a priori, and 353 patients only received IV-tPA. Of these, 44 were excluded for the following reasons: non-MCA stroke (n=36), lacunar stroke (n=4), and miscellaneous (n=4), leaving 309 patients for the present analysis, of which 279 had admission MRI and 30 had CT. The baseline characteristics of the studied population are shown in Table 1. The median (interquartile range) baseline NIHSS score was 15 (9–19), and the mean age was 69±15 years. Occlusion involved the internal carotid artery in 80 patients, including 9 (3%) with isolated internal carotid artery occlusion and 71 with tandem internal carotid artery–MCA occlusion, M1 in 176 (57%) and M2 in 83 (27%), and no occlusion in 35 (11%). The initial arterial status could not be assessed in 6 (2%) patients.

END occurred in 33 (11%) patients. Identified causes were sICH in 6 (2%) and early swelling in 4 (1%), leaving 23 (7%) patients with END. Parenchymal hematoma type 1 was present on follow-up MRI in 1 END Patient but was judged unrelated to the severe END (13 NIHSS points). No patient deteriorated because of early recurrent ischemic...
stroke. Timing of END\textsubscript{unexplained} after tPA was within 2, 2 to 6, 6 to 12, and 12 to 24 hours in 5, 5, 5, and 8 patients, respectively. Among END\textsubscript{unexplained} patients, 2 had a significant initial improvement (≥4 NIHSS points at 1 hour) followed by neurological deterioration.

### Pretreatment Variables Associated With END\textsubscript{unexplained} in Univariate Analysis

The pretreatment characteristics of patients with and without END\textsubscript{unexplained} and the results of the univariate analyses are presented in Table 1. Patients experiencing END\textsubscript{unexplained} less frequently had prior antiplatelet treatment (P=0.03), and more commonly proximal occlusion (P=0.01), than patients without END. Admission glycemia (P=0.03) was higher, whereas NIHSS score before thrombolysis was lower (P<0.01), in patients with END\textsubscript{unexplained}. Among the 164 patients who had pretreatment PWI, larger DWI–PWI mismatch was associated with END\textsubscript{unexplained} (P=0.03).

### Table 1. Pretreatment Characteristics of the Population and Univariate Relationships With END\textsubscript{unexplained}*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Whole Sample (n=309)</th>
<th>END\textsubscript{unexplained} (n=23)</th>
<th>No END (n=276)</th>
<th>OR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient history</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y (y)</td>
<td>69±14.6</td>
<td>73±12.6</td>
<td>68±14.7</td>
<td>1.29 (0.92–1.82)†</td>
<td>0.15</td>
</tr>
<tr>
<td>Male sex</td>
<td>164 (53)</td>
<td>11 (48)</td>
<td>150 (54)</td>
<td>0.84 (0.35–2.00)</td>
<td>0.69</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>45 (14)</td>
<td>6 (26)</td>
<td>39 (14)</td>
<td>2.42 (0.89–6.59)</td>
<td>0.08</td>
</tr>
<tr>
<td>Current smoking</td>
<td>56 (18)</td>
<td>4 (17)</td>
<td>52 (19)</td>
<td>0.96 (0.31–2.95)</td>
<td>0.94</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>91 (30)</td>
<td>8 (35)</td>
<td>83 (30)</td>
<td>1.39 (0.56–3.45)</td>
<td>0.47</td>
</tr>
<tr>
<td>History of antithrombotic use</td>
<td>99 (32)</td>
<td>2 (9)</td>
<td>97 (35)</td>
<td>0.19 (0.04–0.82)</td>
<td>0.03‡‡</td>
</tr>
<tr>
<td>History of statin use</td>
<td>86 (28)</td>
<td>6 (26)</td>
<td>72 (26)</td>
<td>0.94 (0.36–2.50)</td>
<td>0.91</td>
</tr>
<tr>
<td>History of antihypertensive drug use</td>
<td>173 (56)</td>
<td>14 (61)</td>
<td>150 (56)</td>
<td>1.41 (0.57–3.46)</td>
<td>0.46</td>
</tr>
<tr>
<td><strong>Pretreatment characteristics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NIHSS score (NIHSS)</td>
<td>15 (9–19)</td>
<td>9 (8–14)</td>
<td>15.5 (9–20)</td>
<td>0.89 (0.83–0.96)‡ †</td>
<td>&lt;0.01‡‡</td>
</tr>
<tr>
<td>OTT, min</td>
<td>156 (125–194)</td>
<td>180 (145–205)</td>
<td>155 (125–194)</td>
<td>1.01 (1.00–1.02)§</td>
<td>0.21</td>
</tr>
<tr>
<td>Systolic blood pressure, mmHg</td>
<td>155±23</td>
<td>160±20</td>
<td>154±23</td>
<td>1.12 (0.93–1.34)</td>
<td></td>
</tr>
<tr>
<td>Diastolic blood pressure, mmHg</td>
<td>84±16</td>
<td>86±16</td>
<td>83±16</td>
<td>1.11 (0.86–1.44)</td>
<td>0.43</td>
</tr>
<tr>
<td>Glycemia, mmol/L</td>
<td>6.9±2.4</td>
<td>7.9±3.0</td>
<td>6.8±2.1</td>
<td>1.18 (1.02–1.36)¶</td>
<td>0.03‡‡</td>
</tr>
<tr>
<td><strong>Pretreatment imaging</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proximal occlusion</td>
<td>191 (62)</td>
<td>20 (91)</td>
<td>165 (60)</td>
<td>6.55 (5.00–28.57)</td>
<td>0.01‡‡</td>
</tr>
<tr>
<td>DWI volume, mL</td>
<td>22 (9–60)</td>
<td>16 (11–35)</td>
<td>21 (9–64)</td>
<td>0.87 (0.73–1.03)**</td>
<td>0.10</td>
</tr>
<tr>
<td>PWI volume, mL††</td>
<td>83 (32–130)</td>
<td>84 (47–171)</td>
<td>82 (30–128)</td>
<td>1.03 (0.94–1.13)**</td>
<td>0.54</td>
</tr>
<tr>
<td>DWI–PWI mismatch volume, mL††</td>
<td>41 (17–78)</td>
<td>73 (27–142)</td>
<td>40 (16–76)</td>
<td>1.12 (1.01–1.25)**</td>
<td>0.03‡‡</td>
</tr>
<tr>
<td><strong>TOAST classification</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Large artery atherosclerosis</td>
<td>50 (16)</td>
<td>2 (9)</td>
<td>48 (17)</td>
<td>0.48 (0.11–2.10)</td>
<td>0.33</td>
</tr>
<tr>
<td>Cardioembolic</td>
<td>157 (51)</td>
<td>15 (65)</td>
<td>139 (50)</td>
<td>1.68 (0.68–4.12)</td>
<td>0.26</td>
</tr>
<tr>
<td>Others or undetermined</td>
<td>102 (33)</td>
<td>6 (27)</td>
<td>89 (32)</td>
<td>0.79 (0.30–2.08)</td>
<td>0.63</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; DWI, diffusion-weighted imaging; END, early neurological deterioration without clear mechanism; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; OTT, onset-to-treatment time; PWI, perfusion-weighted imaging; and TOAST, Trial of Org 10172 in Acute Stroke Treatment.

*Categorical variables are expressed as n (%), whereas continuous variables are expressed as mean±SD or median (interquartile range).

†Per 10-year increase. †Per 1-point increase. ‡Per 10-minute increase. §Per 10-mmHg increase. ¶Per 1-mmol/L increase.

#Data available for 265 among 279 patients with admission MRI (MRI data irretrievable in 14 patients).

**Per 10-mL increase.

††Data available for 164 patients (11 END\textsubscript{unexplained} and 153 patients without).

‡‡P<0.05.

Exploratory Multivariate Analysis of Predictors

Mismatch volume was not entered into the model because only 11 END\textsubscript{unexplained} patients had admission PWI. Only NIHSS, prior use of antiplatelets, admission glycemia, and age remained after variable reduction process. To keep the number of variables in the model down to 3 and avoid overfitting, age was subsequently removed because it had the highest univariate P value (P=0.15). With the final model, NIHSS (adjusted OR=0.89; 95% CI, 0.82–0.96; P=0.002 per 1-point increase), prior use of antiplatelets (adjusted OR=0.22; 95% CI, 0.06–0.85; P=0.03), and glycemia (adjusted OR=1.26; 95% CI, 1.06–1.44; P=0.007 per 1-mmol/L increase) were associated with END\textsubscript{unexplained}. The c-statistic of the model was...
Factors Associated With Unexplained END During the First 24 Hours
Clinical and radiological data during the first 24 hours post-treatment are shown in Table 2. There was a trend for significance for median glycemia level during the first day, higher in deteriorating patients ($P=0.06$), whereas there was no association with maximum glycemic change. No patients had episodes of hypoglycemia ($<4$ mmol/L). Mean systolic blood pressure within the first 24 hours was marginally higher in END$_{unexplained}$ patients ($P=0.045$), but maximum blood pressure change was not different between the 2 groups. On post-treatment imaging, END$_{unexplained}$ patients had a significantly higher rate of no recanalization ($P<0.01$). Final exploratory multivariate model including median glycemia, mean systolic blood pressure, and recanalization showed that only no recanalization (adjusted OR=$4.18; 95\%$ CI, 1.28–13.69; $P=0.02$) was associated with END$_{unexplained}$ (c-statistic of the model=0.72). These results were confirmed by internal validation using the bootstrap approach (online-only Data Supplement).

Outcome
END$_{unexplained}$ was associated with poor 3-month outcome as compared with non-END patients in univariate analysis ($P<0.01$; Table 2).

Discussion
This study is the first to assess specifically the incidence of unexplained END within 24 hours after IV-rtPA for AIS. The observed incidence of 7% is sizeable and hence clinically relevant. We also report the first clinical and radiological predictors of 24-hour unexplained END after IV-rtPA, showing a strong protective effect of prior antiplatelet therapy as well as an association with lower admission NIHSS, higher blood glucose and mismatch volume, presence of proximal arterial occlusion, and lack of recanalization.

The incidence of 11% for all-cause END in our study is consistent with 3 recently published series of IV-rtPA–treated patients (reported range, 10%–16%) that used the same END definition.$^{3,5}$ Only 2% had sICH, similar to a recent report also using the SITS-MOST definition.$^{14}$ No patient worsened because of early recurrent ischemic stroke, consistent with its previously reported low incidence.$^{15,16}$ Importantly, unexplained END represented 7% of all IV-rtPA–treated patients with AIS and more than two thirds of all-cause ENDS. Thus, the majority of ENDS have no clear underlying mechanism. Although no previous study of unexplained END after IV-rtPA is available for comparison, an incidence of 10% unexplained END has been reported in nonthrombolysed mild strokes.$^{16}$ Finally, consistent with the available literature,$^{2,4}$ we found unexplained END to be associated with poor outcome. Overall, therefore, most deteriorations occurring within 24 hours post-thrombolysis are unexplained yet predict poor outcome, underlying the need to understand their underlying mechanisms to prevent or treat them. Identifying predictors of this ominous complication was our next objective.

Our choice of potential predictors of END$_{unexplained}$ over and above standard variables such as age and admission NIHSS was guided by its putative mechanisms, notably worsening of perfusion or neuronal function beyond the penumbra attributable to, for example, blood pressure drops or swings, hyperglycemia, and thrombus extension in the context of persistent arterial occlusion.$^9$ Lending support to this mechanism, 3

### Table 2. Post-Treatment Factors and Clinical Outcome Associated With END$_{unexplained}$

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Whole Sample (n=308)</th>
<th>END$_{unexplained}$ (n=22)</th>
<th>No END (n=276)</th>
<th>OR (95% CI)</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physiological data on the first 24 h</td>
<td></td>
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</tr>
<tr>
<td>Mean systolic BP, mm Hg</td>
<td>146±16</td>
<td>152±13</td>
<td>145±16</td>
<td>1.37 (1.01–1.86)$^\dagger$</td>
<td>0.045$^|$</td>
</tr>
<tr>
<td>Mean diastolic BP, mm Hg</td>
<td>79±11</td>
<td>78±11</td>
<td>79±11</td>
<td>0.87 (0.57–1.32)$^\dagger$</td>
<td>0.51</td>
</tr>
<tr>
<td>Median glycemia, mmol/L</td>
<td>6.5±2.0</td>
<td>7.1±2.2</td>
<td>6.3±1.7</td>
<td>1.20 (1.00–1.43)$^\dagger$</td>
<td>0.06</td>
</tr>
<tr>
<td>Systolic BP maximum change, mm Hg</td>
<td>60±19</td>
<td>58±12</td>
<td>60±19</td>
<td>0.95 (0.75–1.21)$^\dagger$</td>
<td>0.67</td>
</tr>
<tr>
<td>Diastolic BP maximum change, mm Hg</td>
<td>42±14</td>
<td>40±14</td>
<td>42±14</td>
<td>0.90 (0.65–1.26)$^\dagger$</td>
<td>0.54</td>
</tr>
<tr>
<td>Glycemia maximum change, mm Hg</td>
<td>2.4±1.9</td>
<td>2.3±1.7</td>
<td>2.4±1.1</td>
<td>1.03 (0.80–1.31)$^\dagger$</td>
<td>0.84</td>
</tr>
<tr>
<td>Post-treatment imaging</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No recanalization§</td>
<td>124 (40)</td>
<td>15 (83)</td>
<td>105 (48)</td>
<td>5.38 (1.52–19.12)$^\dagger$</td>
<td>&lt;0.01$^|$</td>
</tr>
<tr>
<td>Outcome</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>mRS 3 mo $&gt;2$</td>
<td>154 (50)</td>
<td>18 (86)</td>
<td>125 (46)</td>
<td>7.06 (2.03–24.51)$^\dagger$</td>
<td>&lt;0.01$^|$</td>
</tr>
</tbody>
</table>

BP indicates blood pressure; CI indicates confidence interval; END$_{unexplained}$, early neurological deterioration without clear mechanism; mRS, modified Rankin Scale; and OR, odds ratio.

*Note that 1 END$_{unexplained}$ patient received endovascular therapy immediately after deterioration and was therefore excluded from this analysis which therefore has 1 patient less for both the whole and END$_{unexplained}$ samples.

$^\dagger$Per 10 mmHg increase.

$^\|$Per 1 mmol/L increase.

§Data available for 242 patients.

¶Data available for 303 patients.

$^{\dagger}P<0.05.$
recent studies have reported the occurrence of new or expanding DWI lesions within, or associated with, larger volumes of asymptomatic tissue in a sizeable fraction of patients with AIS,18–20 shown in one to impact clinical course negatively.18 However, whether END was associated with these observations was not reported.

Our findings strongly suggest that prior use of antiplatelet treatment may afford protection against ENDunexplained. One previous study reported a similar finding but included sICH,1 which in fact strengthens the idea that prior antiplatelet use protects against unexplained END. Our finding is also consistent with another study assessing 3-month outcome.21 Thus, antiplatelets may protect against thrombus extension and same-territory recurrent embolization,22 as well as against recurrences.5

Consistent with studies on all-cause END after thrombolysis,4–11 higher admission glycemia was the second strongest predictor of unexplained END. This association could be accounted for by increased brain lactate production precipitating severely hypoperfused tissue into infarction24 and disrupting cell metabolism within mildly hypoperfused tissue, causing it to become symptomatic. Of note, however, a recent trial found that insulin therapy did not influence infarct growth despite significantly attenuating brain lactate increases.25 Interestingly, hyperglycemia also has prothrombotic effects, hindering recanalization after IV-rtPA26 and perhaps also facilitating thrombus extension.

A third robust predictor of ENDunexplained was lower admission NIHSS score, again consistent with 1 previous report.5 This association might not only represent the ceiling effect intrinsic to this scale, preventing high scores from further escalating, but also reflect the increasingly reported risk of early deterioration in minor strokes, especially when associated with proximal occlusion10,27

Finally, consistent with 2 previous reports,24 proximal occlusion was predictive of ENDunexplained as was also larger mismatch. Both factors may actually be related in that proximal occlusion entails larger hypoperfused volumes,25 in turn exposing to the risk of secondary worsening. In contrast, in the only previous study that directly assessed this relationship, END was associated with smaller DWI–PWI mismatch.29 However, in this study, END was assessed at 48 hours, and in 5 of the 7 index patients, it was clearly related to malignant edema, entailing a large core and hence smaller mismatch.29 The relationship between mismatch volume and END may therefore change over time, further emphasizing the need to consider END within the first 24 hours as a separate clinical entity.

**Associated Factors During the First 24 Hours**

Lack of recanalization at 24 hours was strongly associated with ENDunexplained, consistent with 1 study of all-cause END30 and further strengthening the already discussed critical role of intracranial hemodynamics. There was also a strong trend for an association with higher glycemia during the first day, perhaps via the mechanisms discussed above. Although glycemic swings and episodes of (iatrogenic) hypoglycemia may also contribute to neuronal death, the former was not found to be associated with ENDunexplained while the latter never occurred.

Taking together all the above findings, our study suggests that, in a background of persistent occlusion and extensive mismatch, disruptions in local perfusion pressure secondary to thrombus extension or distal embolization together with high blood glucose at onset of ischemia play an important role in ENDunexplained after IV-rtPA. Early endovascular therapy, which allows higher rates of recanalization, may therefore be an attractive option for patients at high risk of, or experiencing, ENDunexplained.

Our study has limitations. First, we elected a change of ≥2 NIHSS points to define END because smaller changes could be affected by limited reliability, especially for high scores.31 Although widely used, this cutoff is somewhat deliberate and its functional significance may differ with stroke severity. To address this, we performed a post hoc sensitivity analysis using a relative change of ΔNIHSS ≥30% as alternative cutoff, whereby END reflects a larger absolute increase for high than for low baseline scores. This did not substantially change the results (data not shown). Second, although our sample size of IV-rtPA–treated patients with AIS was large, the actual number of ENDunexplained cases was relatively small, which limits the interpretation of the multivariate analyses. For instance, to reduce the risk of overfitting, age was removed as predictor because it had lowest univariate P value, yet including it in a model with 4 variables did not change the findings (data not shown). Of note, the internal validation using bootstrap analysis strengthened the overall multivariate results. Nevertheless, mild associations between some baseline variables and ENDunexplained may also have been missed. Last, our findings do not apply to END after endovascular therapy, which was a cause of a priori exclusion for this study.

Additional multicenter studies involving larger samples are warranted to confirm our findings, which if confirmed could lead to novel approaches to prevent post-thrombolysis END in high-risk patients.

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**Disclosures**

None.

**References**


Unexplained Early Neurological Deterioration After Intravenous Thrombolysis: Incidence, Predictors, and Associated Factors
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SUPPLEMENTAL MATERIAL

Supplemental Methods

Clinical data

Demographics, cigarette smoking, diabetes mellitus, atrial fibrillation, current treatment, systolic and diastolic blood pressure (BP), glycemia at admission and onset-to-treatment time (OTT) were prospectively recorded. The following post-treatment variables were also prospectively collected: BP (monitored every 15mins for the first hour post-treatment then every hour for 24hrs) and capillary glycemia (recorded at 4, 8, 16 and 24hrs). Subcutaneous insulin was administered each 4hrs if glycemia was >10mmol/L. Maximum changes between admission BP or glycemia and their lowest measure during the first 24hrs were calculated. The stroke mechanism was determined according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification.

Supplemental Results

Findings from the internal validation, using bootstrap analyses

Exploratory multivariate analysis of unexplained END predictors: The median ORs (95%CI) based on 1,000 bootstrap replications for this final multivariate model were 0.88 (0.83-0.93), 0.19 (0.04-0.53) and 1.25 (1.06-1.46) for NIHSS (per 1 point-increase), prior use of antiplatelets, and glycemia (per 1 mmol/L increase), respectively, with a median c-statistic of 0.80 (IC95%: 0.71-0.87).

Factors associated with unexplained END over the first 24hrs: The median ORs (95%CI) based on 1,000 bootstrap replications for this final multivariate model were 1.12 (0.99-1.41), 1.02 (0.99-1.05) and 4.43 (1.67-24.98) for median glycemia (per 1mmol/L increase), median systolic BP (per 10mmHg increase) and no recanalization, respectively. The median c-statistic of the model was 0.74 (IC95% 0.62-0.85).
静脉溶栓后不明原因早期神经功能恶化

Incidence, Predictors, and Associated Factors

Pierre Senerès, MS*, Guillaume Ture, MD*, Marie Tisserand, MD, Laurence Legrand, MD, Marc-Antoine Labeyrie, MD, David Calvet, PhD, Jean-François Meder, PhD, Jean-Louis Mas, MD, Catherine Oppenheim, PhD, Jean-Claude Baron, ScD

背景和目的: 静脉溶栓后早期神经功能恶化(early neurological deterioration, END)是一种严重临床事件,与预后不良密切相关。虽然血流动力学以及代谢因素是可能的潜在机制，但是目前尚没有证明其确切原因。静脉溶栓后不明原因 END 的发生率、预测因子及相关因素目前尚未知,这也是本研究的目的。

方法: 从我们的前瞻性数据库中提取了自 2003 年 1 月至 2013 年 3 月期间因急性缺血性卒中(AIS)静脉应用重组组织型纤溶酶原激活剂(IV-rtPA)治疗后 24 小时内临床症状变化的患者。我们分析了 309 例连续入组,发病小于 4.5 小时静脉溶栓的前循环脑梗塞患者。不明原因 END 定义为 24 小时内美国国立卫生研究院卒中量表(NIHSS)评分恶化≥ 4 分,且其影像学未发现确切的机制。采用单变量 logistic 回归分析,比较不明原因 END 与无 END 患者,治疗前的临床及影像学(包括核磁共振弥散加权及弥散/灌注不匹配体积)数据以及治疗后 24 小时的临床数据(如血压、血糖以及核磁共振弥散加权成像)。

结果: 总共 23 例 END 患者,其中 20 例 (83%) 患者为不明原因 END。不明原因 END 与 3 个月时不良预后相关(p<0.01)。表 3. 血管成功再通后出现功能依赖的情况(时间间隔)

<table>
<thead>
<tr>
<th>变量</th>
<th>患者/总人数 (95% CI)</th>
<th>P值</th>
</tr>
</thead>
<tbody>
<tr>
<td>每增加5分 NIHSS评分</td>
<td>1.41 (1.15-1.73)</td>
<td>0.008</td>
</tr>
<tr>
<td>每延迟30min症状开始至首个装置通过, min</td>
<td>1.31 (1.01-1.70)</td>
<td>0.035</td>
</tr>
<tr>
<td>每延迟30min症状开始至腹股沟穿刺, min</td>
<td>1.78 (1.31-2.41)</td>
<td>0.044</td>
</tr>
</tbody>
</table>

结论: 静脉溶栓后不明原因早期神经功能恶化发生率、预测因子及相关因素

Unexplained Early Neurological Deterioration After Intravenous Thrombolysis

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研究人群

根据既往研究的 IAT 后 END, 此 END 定义为发病后 24 小时内。NINDS 分级为 ≥4 分, 第一个 24 小时内判断无好转的患者。血糖升高、脑内出血、患者 END 的临床和影像学数据以及 TOAST 分型在相关研究中已得到广泛认可, 但是目前 END 临床研究多采用 SITS-MOST 研究的定义。患者没有因近期缺血性卒中再发而接受溶栓治疗。对照组中也采取相似的定义。仅 2% 患者发生 sICH, 类似于最近一项研究报道。其他溶栓相关的全因 END 研究也表明, 研究组和对照组的研究终点有所不同。目前的定义中, 无 END 仅包括因低血压的患者。治疗后 24 小时内的 END 终点定义为出现新的神经功能缺损, 提示由原来未受影响的血管域所致。因此, 不明原因 END 定义为除外以上原因推测的近端延伸或远端栓塞。因此, 不明原因 END 被定义为同源性 END 之外和所致脑出血的定义与建议 (RCSIA) 影像学分类的脑出血发生在 24 小时内 NINDS ≥4 分。如果出现脑血管闭塞或死亡, 作为终点; 在受试者中, 实验组与对照组两组间的血压波动情况无差异。在每个组内, NINDS 分级 <3 分, 随访时为 24 小时, 入院时为 24 小时, 纳入研究的患者, 都考虑在入院时的 NIHSS 评分。基线 NIHSS 评分中位数 (四分位间距) 为 15 (9 – 19), 入院后 24 小时内 NIHSS 评分中位数为 16 (12–21)。结果发现仅无血管再通 (校正后 OR=0.19; 95% CI=0.04–0.82) 与不明原因 END 相关。在减少变量后的分析中, 我们还发现大动脉粥样硬化型 TOAST 分型与其他 END 之间也有显著相关(p=0.002)。我们还发现年龄与不明原因 END 之间存在显著相关性(p=0.002)。进一步分析显示, 导致不明原因 END 的原因包括大动脉粥样硬化型 TOAST 分型以及年龄。我们的最终模型中, 描述了 1000 分析, 重复了探索性多因素分析的预测因素。通过内部验证(见表 1), 在探索性多因素分析中, 我们还发现性激素水平、血糖水平以及年龄显著相关。随即我们选取了所有分析中相关的因素, 以及探索性多因素分析中相关的因素, 经内部验证(见表 1), 进行了内部有效性验证(详见在线补充数据)。这些结果均经过源码分析, 进行了内部有效性验证。我们使用了 SAS Institute Inc, Cary, NC 和 SPSS 16.0 (SPSS Inc) 进行统计分析。首先, 我们使用了单因素分析, 发现了 1000 分析, 我们还发现性激素水平、血糖水平以及年龄显著相关。随即我们选取了所有分析中相关的因素, 以及探索性多因素分析中相关的因素, 经内部验证(见表 1), 进行了内部有效性验证(详见在线补充数据)。这些结果均经过源码分析, 进行了内部有效性验证。我们使用了 SAS Institute Inc, Cary, NC 和 SPSS 16.0 (SPSS Inc) 进行统计分析。
纳入303例患者数据。每增加10-mm Hg舒张压最大变化, m.mol/L

备注

1例不明原因 END患者在出现恶化后立即接受了血管内治疗,因此剔除此分析。

3个月mRS >2

无血管再通

治疗后影像

血糖最大变化, mmol/L

舒张压最大变化, mm Hg

收缩压最大变化 , mm Hg

平均血糖, mmol/L

平均舒张压, mm Hg

平均收缩压, mm Hg

首个24小时的相关因素

基线特征 患者总数

表2. 治疗后因素及与不明原因 END*相关的临床结局

首个 24 小时的相关因素

患者早期恶化的风险增加,尤其是近段血管闭塞的患者。END 作为一个独立的临床病症。较大的梗死核心及较小的不匹配区域。不匹配体积与 END 之间的关系

小时内的患者,7例 END 患者中的5例明显是与恶性水肿相关,伴有

于屏气初期及末期记录平均脑血流速度(mean cerebral flow velocities, MFVs)。通过二氧化碳监测仪测量出呼吸暂停的确切

一经验丰富的超声检查工作者不知晓

受试者如有根据国际指南定义的高血压病,糖尿病或高脂血症,则记录于病历或目前药物治疗中

病史回顾及

终期峰值流速比值

于 2003 年 1 月至 2010 年 8 月进行。受试者已于一级预防项目中通过

超声筛查颈动脉粥样硬化疾病,由于其血管风险而被其初级保健医生

功能损害可能的发病机制, 我们评价了脑血管反应性 (cerebrovascular reactivity,CVR)用以衡量脑血流动力学状态,以及颈总动脉壁厚度

超声检查

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