Conclusions}

114.005426/-/DC1.

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 (ENDunexplained).

Methods—We analyzed 309 consecutive patients thrombolysed intravenously ≤4.5 hours from onset of anterior circulation stroke. ENDunexplained was defined as a ≥4-point deterioration on 24-hour National Institutes of Health Stroke Scale, without definite mechanism on concomitant imaging. ENDunexplained 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 ENDunexplained ENDunexplained was associated with poor 3-month outcome (P<0.01). In univariate analysis, admission predictors of ENDunexplained 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 ENDunexplained in multivariate analysis (P=0.02).

Conclusions—ENDunexplained 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;45:00-00.)

Key Words: stroke ■ thrombolytic therapy

A
fter intravenous recombinant tissue-type plasminogen activator (IV-rtPA) for acute ischemic stroke (AIS), clinical evolution in the first 24 hours is largely unpredictable,1 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,2–5 it is important to prevent or treat this detrimental event. However, many uncertainties still preclude its informed management. First, estimates of its incidence vary widely,2–5 depending on clinical definition and time window used.6 Second, although some ENDs have a clear cause such as symptomatic intracerebral hemorrhage (sICH), malignant edema, and early recurrent ischemic stroke, leading to evidence-based management,7 no clear cause is found in the rest, a clinical category sometimes referred to as progressive stroke.8 This study focuses on this category of post-thrombolysis END for which no underlying mechanism for the worsening of the initial neurological deficit is identified, to be operationally referred to as ENDunexplained in what follows.

There are currently no management guidelines for post-thrombolysis unexplained END, and in routine clinical practice,
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 nonthrombolyzed AIS, which may not generalize to the IV-rtPA setting. Thus, the incidence, predictors, and associated factors of post-thrombolysis END_{unexplained} are still largely unknown and are the topic of the present work.

Methods

Patients

We extracted all consecutive patients who received IV-rtPA 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-rtPA 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-rtPA, which is part of routine care.

Imaging Protocol

MRI is systematically implemented as first-line pretreatment work-up in candidates 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 lesions 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 ≥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 ≈27% of contraindicated patients. Filling 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. Recanalization was defined as a thrombolysis in cerebral infarction score ≥2 on follow-up magnetic resonance angiography.

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-rtPA 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 ΔNIHSS ≥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_{unexplained} was operationally defined as END without evidence for any of the above causes or other potentially causative definitive 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_{unexplained} and pre- or post-treatment variables were assessed as odds ratios (ORs) and 95% confidence intervals (95% CIs) in univariate logistic models with END_{unexplained} as the dependent variable. Pre- and post-treatment variables associated with END_{unexplained} in univariate analysis at a level of P<0.20 were candidates for inclusion into a multivariate logistic model. However, n = 1 predictor can be entered into a multivariate logistic regression model for 10 events of the dependent variable. Therefore, considering the relatively small number of END_{unexplained} 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-rtPA. 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_{unexplained}. Parenchymal hematoma type 1 was present on follow-up MRI in 1 END_{unexplained} 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 t\textsubscript{PA} 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 ($\geq 4$ 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} ($P=0.03$).

### 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}.

<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>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>69.1±14.6</td>
<td>73.1±12.6</td>
<td>68.6±14.7</td>
<td>1.29 (0.92–1.82)$\dagger$</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>37 (13)</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>80 (29)</td>
<td>1.39 (0.56–3.45)</td>
<td>0.47</td>
</tr>
<tr>
<td>History of antiplatelet use</td>
<td>99 (32)</td>
<td>2 (9)</td>
<td>92 (34)</td>
<td>0.19 (0.04–0.82)</td>
<td>0.03$\dagger$</td>
</tr>
<tr>
<td>History of statin use</td>
<td>86 (28)</td>
<td>6 (26)</td>
<td>78 (29)</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>152 (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>
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</tr>
<tr>
<td>NIHSS score</td>
<td>15 (9–19)</td>
<td>9 (8–14)</td>
<td>15.5 (9–20)</td>
<td>0.89 (0.83–0.96)$\dagger$</td>
<td>&lt;0.01$\dagger$</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)$\dagger$</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)$\parallel$</td>
<td>0.23</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)$\parallel$</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)$\parallel$</td>
<td>0.03$\ddagger$</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 (1.50–28.57)$\parallel$</td>
<td>0.01$\ddagger$</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$\dagger$</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$\dagger$</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$\ddagger$</td>
</tr>
<tr>
<td><strong>TOAST classification</strong></td>
<td></td>
<td></td>
<td></td>
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</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\textsubscript{unexplained}, 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).
‡‡$P<0.05$. 

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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.18 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 unexplained10 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.2 Lending support to this mechanism, 3
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,16–20 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 antplatelet treatment may afford protection against END unexplained. One previous study reported a similar finding but included sICH,3 which in fact strengthens the idea that prior antplatelet use protects against unexplained END. Our finding is also consistent with another study assessing 3-month outcome.21 Thus, antplatelets may protect against thrombus extension and same-territory recurrent embolization,22 as well as against reocclusions.5

Consistent with studies on all-cause END after thrombolysis,4,22 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 infarction 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 END unexplained was lower admission NIHSS score, again consistent with 1 previous report.4 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 occlusion.10,27

Finally, consistent with 2 previous reports,24 proximal occlusion was predictive of END unexplained as well as wider mismatch. Both factors may actually be related in that proximal occlusion entails larger hypoperfused volumes,28 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.28 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 END unexplained, 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 END unexplained, 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 END unexplained 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, END unexplained.

Our study has limitations. First, we elected a change of ≥4 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 END unexplained 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 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 END unexplained 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.

**Acknowledgments**

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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
发生率、预测因子及相关因素

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

Pierre Sener, MSc*; Guillaume Turc, MD*; Marie Tisserand, MD; Laurence Legrand, MD; Marc-Antoine Labeye, MD; David Calvet, PhD; Jean-Francois Meder, PhD; Jean-Louis Mas, MD; Catherine Oppenheim, PhD; Jean-Claude Baron, ScD

背景和目的
前循环卒中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，但是目前尚没有证据支持。静脉应用重组组织型纤溶酶原激活剂（IV-rtPA）治疗后 24 小时内临床变化很难预测，有必要对这个时间窗口进行更好的观察研究。虽然 AIS 患者大多数在 IV-rtPA 后症状得到改善，但有部分患者出现了早期神经功能恶化（END）。而 END 预示着预后不良，所以预防或处理这种不良临床事件很重要。但是尚有许多不确定因素，以致无法进行有效性管理。首先，END 的发生率不明，次之，需分析该事件发生都有重要的意义。

急性期卒中患者中（AIS）静脉应用重组组织纤溶酶原激活剂（IV-rtPA）治疗后 24 小时内临床恶化很难预测，有必要对这个时间窗口进行更好的观察研究。虽然 AIS 患者大多在 IV-rtPA 治疗后症状得到改善，但有部分患者出现了早期神经功能恶化（END）。而 END 预示着预后不良，所以预防或处理这种不良临床事件很重要。但是尚有多种不确定因素，以致无法进行有效性管理。首先，END 的发生率不明，次之，需分析该事件发生都重要的意义。

数据校正了年龄、性别和基线 NIHSS 评分。每增加 5 分 OR 或 P 值
NIHSS 评分
≥20
11–19
8–10
≤6
NIHSS 评分
†
每增长 10 岁 OR 或 P 值
>80
70–80
≤60
年龄
* 数据校正了年龄、性别和症状开始至再灌注时间。数据校正了基线 NIHSS 评分、性别和症状开始至再灌注时间。

每延迟 30 分钟 OR 或 P 值
421–570
271–420
105–240
症状开始至再灌注,min
每延迟 30 分钟 OR 或 P 值
376–510
241–375
105–240
症状开始至首个装置通过,min
每延迟 30 分钟 OR 或 P 值
346–480
211–345
105–240
症状开始至腹股沟穿刺,min

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>
<th>变量</th>
<th>患者/总人数 (95% CI)</th>
<th>P 值</th>
</tr>
</thead>
<tbody>
<tr>
<td>血管成功再通时间</td>
<td></td>
<td></td>
<td>血管成功再通时间</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤10 分钟</td>
<td>20/37 (54)</td>
<td></td>
<td>&gt;10 分钟</td>
<td>25/39 (64)</td>
<td></td>
</tr>
<tr>
<td>10–20 分钟</td>
<td>55/103 (54)</td>
<td></td>
<td>20–30 分钟</td>
<td>25/36 (72)</td>
<td></td>
</tr>
<tr>
<td>&gt;30 分钟</td>
<td>28/44 (64)</td>
<td></td>
<td>&gt;30 分钟</td>
<td>28/44 (64)</td>
<td></td>
</tr>
</tbody>
</table>

表 4. 血管成功再通后出现功能依赖的情况（年龄和 NIHSS 评分）

<table>
<thead>
<tr>
<th>变量</th>
<th>患者/总人数 (95% CI)</th>
<th>P 值</th>
<th>变量</th>
<th>患者/总人数 (95% CI)</th>
<th>P 值</th>
</tr>
</thead>
<tbody>
<tr>
<td>年龄*</td>
<td></td>
<td></td>
<td>年龄*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤61</td>
<td>14/24 (58)</td>
<td></td>
<td>&gt;61</td>
<td>13/22 (59)</td>
<td></td>
</tr>
<tr>
<td>61–70</td>
<td>25/39 (64)</td>
<td></td>
<td>70–80</td>
<td>29/53 (55)</td>
<td></td>
</tr>
<tr>
<td>&gt;80</td>
<td>27/51 (54)</td>
<td></td>
<td>&gt;80</td>
<td>27/51 (54)</td>
<td></td>
</tr>
</tbody>
</table>

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不明原因 END 定义为除外以上原因或在影像学上出现 END。我们首次报道了 IV-rtPA 后 24h 内发生不明原因 END 的临床及影像学数据。通过影像学分析,我们发现在 IV-rtPA 治疗的队列研究中,约 10%的患者可能发生不明原因 END。这项研究的发现也提示我们,对于 AAS 患者,应尽可能避免应用 IV-rtPA。在少数情况下,如果治疗的获益大于风险,则应考虑使用 IV-rtPA。然而,由于这项研究的样本量较小,结果可能不具代表性。因此,我们需要进行更大样本量的随机对照试验,以进一步验证这项研究的发现。
表1: 患者基线特征

<table>
<thead>
<tr>
<th>基线特征</th>
<th>患者总数</th>
<th>END数</th>
<th>OR (95% CI)</th>
<th>P值</th>
</tr>
</thead>
<tbody>
<tr>
<td>年龄,岁</td>
<td>63±14</td>
<td>64±14</td>
<td>1.03 (0.80–1.31)</td>
<td>0.67</td>
</tr>
<tr>
<td>性别,男</td>
<td>224 (73)</td>
<td>157 (50)</td>
<td>1.37 (1.01–1.86)</td>
<td>0.045</td>
</tr>
<tr>
<td>血压,收缩压, mm Hg</td>
<td>146±16</td>
<td>145±16</td>
<td>0.90 (0.65–1.26)</td>
<td>0.51</td>
</tr>
<tr>
<td>血压,舒张压, mm Hg</td>
<td>79±11</td>
<td>79±11</td>
<td>0.87 (0.57–1.32)</td>
<td>0.51</td>
</tr>
</tbody>
</table>

**结果: **纳入303例患者数据。

每增加1-mmol/L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

首个24小时的生理数据

BP血压; CI 可信区间; 不明原因 END, 原因不明的早期神经功能恶化; mRS, 改善Rankin评分; OR优势比.

**讨论:**

最近，与既往两项研究结果一致，近段血管闭塞与缺血半暗带体影响 MMSE 分值下降的风险随着 BHI 异常的增加而逐渐增高，双侧屏气指数均异常的患者风险最高 (P<0.0001)。颈动脉内中膜厚度不影响 END 分值。

最终, 本研究结果与既往关于无症状性双侧颈动脉重度狭窄与认知恶化的研究结果一致。通过彩超评估 CVR 功能改善性治疗, 有助于推导出预防溶栓后高危患者发生 END 的新方法。

**方法:**

该前瞻性研究由马尔凯理工大学神经病学诊所的血管超声实验室推荐纳入。

**结论:**

无症状性双侧颈动脉重度狭窄与认知恶化

无显著性双侧颈动脉重度狭窄的患者管理存在争议。没有明确的证据表明任何疗法的改变是对改变患者结局是最佳的。也

- 增加 END 的患者数较小, 这限制了多因素回归分析的阐释说明。例如, 为

- 敏感性分析, 采用一个相对变化 ΔNIHSS ≥ 30%作为一选择性界值,

- 对于不明原因 END 风险较高或已发生的患者可考虑介入治疗。早期血管内中膜厚度分界值为 1.0mm。

- 颈动脉粥样硬化疾病的患者可出现认知功能的轻度减退, 有时因个体变化而轻重不一的有益的治疗效果。

**参考文献:**


