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Early neurological stability predicts adverse outcome after acute ischemic stroke

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Abstract

Background: Deterioration in the National Institutes of Health Stroke Scale (NIHSS) in the early days after stroke is associated with progressive infarction, brain edema, and/or hemorrhage, leading to worse outcome.

Aims: We sought to determine whether a stable NIHSS score represents an adverse or favorable course.

Methods: Brain magnetic resonance images from a research cohort of acute ischemic stroke patients were analyzed. Using NIHSS scores at baseline and follow-up (day 3–5), patients were categorized into early neurological deterioration (ΔNIHSS ≥ 4), early neurological recovery (ΔNIHSS ≤ -4) or early neurological stability (ΔNIHSS between -3 and 3). The association between these categories and volume of infarct growth, volume of swelling, parenchymal hemorrhage, and 3-month modified Rankin Scale score were evaluated.

Results: Patients with early neurological deterioration or early neurological stability were less likely to be independent (modified Rankin Scale = 0–2) at 3 months compared to those with early neurological recovery ($P < 0.001$). Patients with early neurological deterioration or early neurological stability were observed to have significantly greater infarct growth and swelling volumes than those with early neurological recovery ($P = 0.03$; $P < 0.001$, respectively). Brain edema was more common than the other imaging markers investigated and was independently associated with a stable or worsening NIHSS score after adjustment for age, baseline stroke volume, infarct growth volume, presence of parenchymal hemorrhage, and reperfusion ($P < 0.0001$).

Conclusions: Stable NIHSS score in the subacute period after ischemic stroke may not be benign and is associated with tissue injury, including infarct growth and brain edema. Early improvement is considerably more likely to occur in the absence of these factors.

Keywords

Outcome, secondary neurological injury, ischemic stroke, magnetic resonance image, edema, deterioration

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Introduction

In patients suffering acute stroke, the degree of neurological deficit frequently changes after initial presentation.[1] The evolution of neurological impairment in the early days after stroke onset influences long-term outcome.[2] Accordingly, the subacute National Institutes of Health Stroke Scale (NIHSS) score following stroke is a stronger predictor of long-term global disability than the baseline score.[3]

Prior studies have focused on the implications of dramatic worsening after stroke,[4–6] termed early neurological deterioration (END), and commonly defined as

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an increase of ≥4 in the NIHSS.[1,7,8] Up to one-third of stroke patients experience END,[3,6] although the frequency varies with the precise definition used.[9] The relationship of END with secondary tissue injury and poor long-term outcome is well established.[5,6,10–12] In contrast, less is known about patients with early neurological stability (ENS), who exhibit a stable neurological exam in the subacute period.

Understanding the factors that predict subacute deficit changes can advance prognostication and may identify putative therapeutic targets to improve long-term outcome. Several factors have been postulated to contribute to secondary neurological injury such as brain edema[6,13], infarct growth[2,12,14,15], parenchymal hemorrhage (PH)[4,10], revascularization status[16,17], and metabolic factors including hyperglycemia[5,10,11,18,19]. Recent MRI-based methods can distinguish and quantify several of these processes in a wide array of stroke severity.[20]

Aims and hypothesis

In this study, we sought to determine whether subacute stability in neurological deficit, ENS, was a sign of uneventful recovery or unrecognized injury. We also sought to characterize the relative contributions of brain edema, infarct growth, PH, and revascularization to early neurological course after stroke. We hypothesized that ENS and END are both adverse clinical manifestations of secondary tissue injury.

Methods

Patient characteristics

Patients enrolled in the Echoplanar Imaging Thrombolysis Evaluation Trial (EPITHET, NCT00238537) were analyzed. Details of the cohort have been previously described.[21] In brief, the EPITHET study enrolled acute hemispheric ischemic stroke patients who presented 3–6 h after symptom onset, with an NIHSS score greater than 4. Magnetic resonance imaging (MRI), magnetic resonance angiography (MRA), perfusion-weighted imaging (PWI), and NIHSS assessments were performed at baseline and day 3–5. Long-term outcome was measured with 90-day modified Rankin Scale (mRS) score, with good outcome defined as mRS of 0–2 and poor outcome as mRS of 3–6.[21]

EPITHET patients lacking day 3–5 MRI or PWI, or patients with DWI of insufficient quality were excluded from the present analysis. The Institutional Review Board approved this study, and all patients or their legally authorized representative originally provided informed consent.

Early neurological deterioration, stability, and recovery

The change in NIHSS (ΔNIHSS) was derived for each subject by subtracting follow-up NIHSS from the baseline score. In accordance with prior literature, we defined END as an increase of ≥4 points and early neurological recovery (ENR) as a decrease of ≥4 points.[1,4,8,11] Patients with ΔNIHSS values between −3 and 3 were considered to have ENS.

Imaging analysis

Region-of-interest (ROI) analysis was conducted as previously described,[20,22] using a semi-automated method in Analyze 11.0 (Biomedical Imaging Resource, Rochester, MN). Baseline and follow-up stroke ROIs were outlined on DWI. Lesion volumes were determined and the change in total lesion volume (ΔDWI) from baseline to follow-up was calculated. The component volumes attributable to brain edema, infarct growth, and PH were determined for each subject by comparing baseline and follow-up scans. These variables were distinguished and quantified using previously described methodology[20,22] (see Supplementary Figure 1 for demonstration of this imaging analysis approach).

New areas of infarction (not present on the baseline DWI) were identified on follow-up DWI. The presence of PH (defined as PH1 and PH2) was based on the designation from the original EPITHET report.[21] PH volume was quantified in Analyze 11.0. Swelling volumes were calculated based on the relationship: swelling volume = ΔDWI volume − infarct growth volume − PH volume. Each variable was also dichotomized and analyzed for association with poor outcome. Swelling volume was dichotomized at >11 mL and infarct growth at ΔASPECTS score >2 based on thresholds previously demonstrated to predict clinical outcome.[20] Hemorrhagic transformation (HT) was dichotomized based on the presence or absence of PH.[23]

Revascularization was assessed by reperfusion and recanalization measures.[24,25] Reperfusion was defined as >90% reduction in the volume of the perfusion-weighted imaging deficit between baseline and day 3–5, as previously reported.[21] To assess recanalization, we evaluated vessel occlusion status between baseline and day 3–5 MRA. We defined persistent occlusion as the continued presence of occlusion at the same site between baseline and follow-up MRA, partial recanalization as an improvement in the degree of obstruction without complete resolution, and complete recanalization as normal follow-up MRA that was occluded at baseline. Finally, a normal study had a patent MRA at baseline and follow-up.

Statistical analysis

Differences between ENR, ENS, and END groups were analyzed using the Fisher's exact or chi-squared test for binary variables, and ANOVA or Kruskal–Wallis testing for continuous variables. Univariate regression was performed to investigate the association between imaging variables and ΔNIHSS. Multivariate linear regression modeling was performed to assess the independent effects of swelling, infarct growth, HT, and reperfusion status on continuous ΔNIHSS score. To evaluate for collinearity in this model, Variable Inflation Factor (VIF) and correlation of the estimate values were generated. These data are provided in the Supplementary Material. Using multivariate logistic regression, we also compared predictors of ENR versus ENS combined with END. All tests were two-sided and performed with the threshold for significance set at $P < 0.05$ using JMP Pro 11.0 (SAS Institute, Cary, NC).

Results

Study population

Of 101 subjects enrolled in the EPITHET study, 75 were included in the present analysis. Thirteen patients were excluded because of insufficient DWI quality, 11 had no follow-up MRI, and 2 had no follow-up NIHSS assessment. Of patients included in this investigation, 31 had ENR (41%), 36 had ENS (48%), and 8 had END (11%). The clinical characteristics of each group are reported in Table 1. The groups were similar in age, comorbidities, and admission NIHSS. Patients exhibiting ENR had smaller baseline stroke lesions on DWI ($P = 0.02$) and were more likely to have experienced reperfusion ($P = 0.0002$).

ENS and functional outcome

We found that ΔNIHSS was independently associated with 90-day mRS score after adjustment for age, sex, baseline NIHSS, baseline stroke volume, and admission blood glucose levels ($P < 0.001$; see Supplemental Table 1). Poor functional outcome was common in patients with ENS (75%) and END (100%) as compared to those with ENR (25%) (Figure 1, $P < 0.001$).

ENS is associated with secondary tissue injury

Patients with and without PH had differing ΔNIHSS (2 ± 7 versus -3 ± 5, respectively, $P = 0.006$). Accordingly, patients exhibiting ENR had a lower incidence of PH (3%, $P = 0.04$) versus ENS (19%) and END (25%) (Figure 2(a)).

Larger infarct growth was associated with ΔNIHSS ($\rho = 0.34$, $P < 0.005$). In accord, Figure 2(b) demonstrates that median infarct growth volume was smaller in patients with ENR relative to ENS and END (Kruskal–Wallis test, $P = 0.03$).

Figure 2(c) demonstrates a stepwise increase in swelling volume in patients with ENR (7 ± 4 mL), compared with those with ENS (32 ± 4 mL) and END (48 ± 8 mL; ANOVA, $P < 0.0001$). When dichotomized at the threshold of > 11 mL, swelling was evident in only 16% of patients with ENR, but in 69% of those with ENS and 63% of those with END ($P < 0.0001$, Figure 2(d)).

Supplementary Figure 2 depicts the relative frequency of each type of secondary injury in patients with ENS and END combined. Swelling was evident in 68% of patients, whereas PH and infarct growth were evident in 20% and 25%, respectively. Swelling alone, without co-association of PH or infarct growth, was observed in 32% of patients. Infarct growth and PH alone were each observed in 2% of patients. Only 27% of patients who experienced ENS or END did not have PH, infarct growth, or swelling.

Next, we evaluated the effect of revascularization (e.g. reperfusion and recanalization), which is consistently associated with good outcome.[26–29] Reperfusion was observed frequently with ENR (69%), less frequently with ENS (22%), and rarely with END (13%) ($P < 0.001$). Similarly, recanalization was exhibited by 36% of patients with ENR, by 9% with ENS and 0% with END ($P < 0.001$).

Independent predictors of early neurological course

We next developed a multivariate model to investigate independent predictors of early change in NIHSS. We incorporated the imaging markers of secondary injury in addition to previously reported predictors of ΔNIHSS, including admission glucose, baseline DWI lesion volume, and reperfusion status.[5,6,10,12,30] Of these, only swelling volume and reperfusion independently predicted ΔNIHSS (Table 2, model 1). These results were unchanged when substituting recanalization status for reperfusion (Supplementary Table 4). To assess for multicollinearity in Multivariate Model 1, VIF and correlation of the estimates values were generated. All VIF values were below 10, with none exceeding 2.75. This, in conjunction with low correlation between included predictors, supports an absence of multicollinearity in the model (see Supplementary Tables 2 and 3).

Because our results suggested that ENS and END represent a similar adverse neurological course, we dichotomized ΔNIHSS into ENR versus ENS and END. In multivariate logistic regression, swelling

Table 1. Clinical and imaging characteristics of the EPITHET cohort

	ENR (n = 31)	ENS (n = 36)	END (n = 8)	*P* value
Age (years), mean ± SD	71 ± 13	73 ± 14	75 ± 8	0.69
Sex, male, n (%)	16 (52)	20 (56)	5 (63)	0.85
Admission MAP (mmHg), mean ± SD	99 ± 12	100 ± 12	106 ± 14	0.55
Admission glucose (mmol/L), median (IQR)	7 (6–8)	7 (6–8)	8 (7–12.5)	0.09
Smoking history, yes, n (%)	11 (35)	15 (42)	3 (38)	0.87
Comorbidities, n (%)				
Diabetes mellitus	6 (19)	8 (22)	3 (38)	0.55
Hypertension	21 (68)	23 (64)	8 (100)	0.13
Hyperlipidemia	17 (55)	12 (33)	4 (50)	0.20
Atrial fibrillation	12 (39)	16 (44)	2 (25)	0.59
IV tPA, n (%)	19 (61)	12 (33)	4 (50)	0.07
Time to IV tPA treatment (min), mean ± SD	293 ± 45	293 ± 50	292 ± 44	0.99
Admission NIHSS, median (IQR)	11 (10–16)	14 (7–18)	12 (10–17)	0.71
Follow-up NIHSS, median (IQR)	3 (2–8)	13 (8–19)	21 (17–24)	<0.0001***
Admission DWI volume (mL), median (IQR)	11 (7–31)	31 (12–69)	23 (10–116)	0.02*
Admission PWI volume (mL), median (IQR)	142 (94–214)	198 (83–257)	208 (101–369)	0.30
Swelling volume (mL), mean ± SD	7 ± 4.2	32 ± 3.9	48 ± 8.2	<0.0001***
Infarct growth volume (mL), median (IQR)	0.9 (0–6)	10 (0–32)	9 (1–40)	0.03*
Parenchymal hemorrhage, n (%)	1 (3)	7 (19)	2 (25)	0.04*
Reperfusion, n (%)	20 (69)	7 (22)	1 (13)	0.0002***

DWI: diffusion-weighted imaging; IV tPA: intravenous tissue plasminogen activator; NIHSS: National Institutes of Health Stroke Scale; MAP: mean arterial pressure; PWI: perfusion-weighted imaging; reperfusion: >90% reduction in perfusion-weighted imaging deficit volume between baseline and day 3–5.
*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

volume and absence of reperfusion were independent predictors of ENS and END (Table 2, model 2).

Discussion

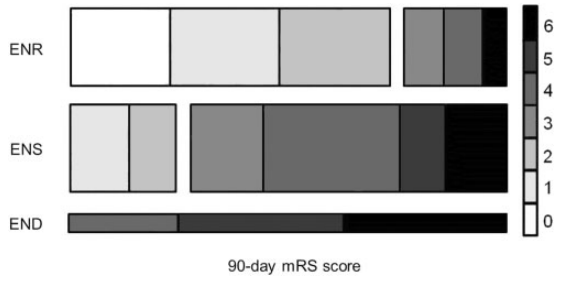
In this study, we report that a stable neurological exam after stroke is an adverse prognostic sign for recovery irrespective of baseline NIHSS score. We find that patients with ENS are at high risk for poor long-term outcome, and that ongoing tissue injury might mediate this association. Furthermore, in this cohort of moderate-to-severe stroke, almost half of patients exhibited ENS. These data underscore the clinical importance of ENS and of studying the factors that may predict its incidence.

Although PH was associated with END and ENS, it was the least common form of secondary injury. Although we hypothesized that PH may lead to ENS or END independently, its frequent co-association with edema made it difficult to study as a separate entity in this cohort.

Infarct growth was associated with END and ENS in univariate analysis; however, it was not an independent predictor of ΔNIHSS. We hypothesize that the association between infarct growth and outcome was mediated by the stronger effect leveraged by reperfusion

in our model. Accordingly, reperfusion was an independent predictor of improving NIHSS score in multivariate analyses. These findings are consistent with prior studies demonstrating the robust clinical benefit of reperfusion.[29,31] That said, it was not the only independent predictor of ΔNIHSS, suggesting that reperfusion does not account for all of the variability in early neurological course. Our analyses reveal that brain edema may be another contributor.

Figure 1. Distribution of 90-day modified Rankin Scale (mRS) scores for patients with early neurological recovery (ENR), stability (ENS), and deterioration (END). The right-hand key represents each category of mRS as labeled. The height of each bar represents the proportion of ENR, ENS, and END in this cohort (41%, 48%, and 11%, respectively).



Brain edema was the most common form of secondary neurological injury, and it occurred in isolation in about one-third of patients. This, in conjunction with our finding that swelling volume independently predicts worsening NIHSS score, suggests that moderate swelling may be a more common form of secondary injury than previously appreciated. Validation in additional cohorts and prospective study would be necessary to establish whether there is any causal link between moderate brain edema and long-term outcome.

Unexplained ENS-END was less common in our study relative to prior reports.[18] Our study accounted for about three quarters of cases. Although this may be explained by increased detection via our imaging methods, alternatives such as differences in cohort severity and/or treatment rates with IV tPA are also possible. The unaccounted for sources of ENS-END may

Figure 2. Association of early neurological course with markers of secondary injury. (a) Parenchymal hemorrhage (PH) is more common in patients with early neurological stability (ENS) and deterioration (END) than in those with early neurological recovery (ENR; $P = 0.04$). (b) There is a significant difference in infarct growth in patients among the three categories (*$P = 0.03$). (c) Swelling volume demonstrates a stepwise association with ENR, ENS, and END (ANOVA; ***$P < 0.0001$). (d) Subjects with swelling volumes > 11 mL were significantly more likely to have ENS or END than ENR ($P < 0.0001$).

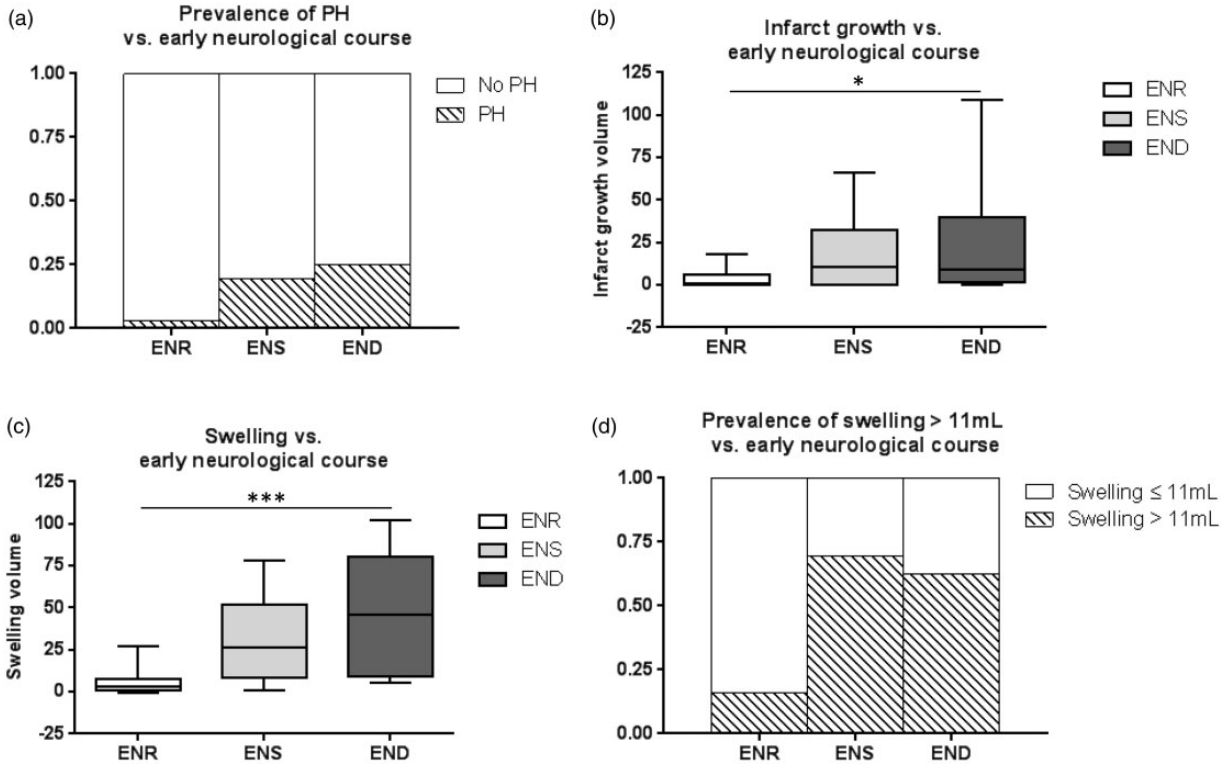


Table 2. Univariate and multivariate predictors of change in NIHSS from baseline to day 3–5

	Univariate analyses			Multivariate model 1			Multivariate model 2		
	ΔNIHSS			ΔNIHSS $R^2 = 0.44$			ENR vs. ENS+END $R^2 = 0.38$, $AUC = 0.881$		
	β	95% CI	*P* value	Adjusted β	95% CI	*P* value	Adjusted OR	95% CI	*P* value
Age	0.027	−0.078 to 0.13	0.61						
Admission glucose	5.96	2.07–9.85	0.055	3.54	−0.57 to 7.66	0.09			
Admission DWI	3.04	0.40–5.67	0.0043**	−0.83	−4.31 to 2.65	0.66			
Infarct growth	2.53	0.76–4.30	0.01*	0.02	−0.02 to 0.05	0.33	0.93	0.26–3.6	0.91
Swelling	0.11	0.071–0.15	<0.0001***	0.10	0.02–0.17	0.007**	0.94	0.88–0.98	0.014*
PH	−2.71	−4.6 to −0.82	0.0055**	−1.26	−2.98 to 0.46	0.15	0.26	0.012–2.3	0.27
Reperfusion	2.6	1.3–4.0	0.0001***	1.37	0.05–2.69	0.043*	4.1	1.2–17	0.036*

Admission glucose and admission DWI volume were log transformed before inclusion in Multivariate model 1. Data are from the Echoplanar Imaging Thrombolysis Evaluation Trial (EPITHET) cohort.

CI: confidence interval; ΔNIHSS: change in National Institutes of Health Stroke Scale score from baseline to day 3–5; DWI: diffusion-weighted imaging; ENR: early neurological recovery; ENS: early neurological stability; END: early neurological deterioration; OR: odds ratio; PH: presence of parenchymal hemorrhage 1 or 2; reperfusion: >90% reduction in perfusion-weighted imaging deficit volume between baseline and day 3–5.

*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

include metabolic effects,[11] systemic complications such as infection,[32] disruptions in local perfusion from thrombus extension,[8,18] or other unknown sources.

Our study has limitations. This was a retrospective analysis performed in a cohort of moderate-to-severe infarction. Our results may not be generalizable to small and/or mild strokes. Second, we used a change of ≥4 NIHSS points to assign individuals to ENR, ENS, and END, based on accepted definitions,[5,7] and to maintain inter-rater reliability.[33] Additionally, our sample size was relatively small, particularly with respect to the END subgroup. The uneven sample sizes of ENR, ENS, and END subgroups may have skewed our results. However, our analysis of ΔNIHSS as a continuous variable avoided these limitations and supports the effect of swelling on early outcome. Finally, although the characteristics of the END subgroup are similar to prior reports,[5,6] the exclusion of 11 patients that lacked day follow-up MRI may have introduced bias into our analyses. These patients may have been more likely to have neurological deterioration preventing imaging from being performed. While this may underestimate the prevalence for each factor on END, it does not affect our main finding that neurological stability represents an equally adverse neurological course in the days after stroke.

Conclusions

Our study identifies ENS as an adverse prognostic sign for recovery after stroke. Ongoing tissue injury, including infarct growth, hemorrhage, and brain edema may manifest as a persistence in the severity of neurological deficit, preventing ENR. Identifying therapeutic strategies to limit the impact of each of these factors may promote both early and long-term recovery.

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