Neurofluctuation in patients with subcortical ischemic stroke

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ABSTRACT

Objective: The purpose of this study was to assess the incidence of deterioration, fluctuation, and associated risk of poor outcome in patients with subcortical stroke (SCS).

Methods: We conducted a prospective observational study, enrolling patients admitted with SCS based on their clinical examination and imaging studies. An NIH Stroke Scale evaluation was performed daily and whenever deterioration in examination was detected. Neurologic deterioration was defined as a motor score increase of at least 1 on the NIH Stroke Scale. Modified Rankin Scale scores at discharge were used to assess outcome.

Results: Among 90 enrolled patients, 37 (41%) deteriorated, 75% of them in the first 24 hours after enrollment. Administration of tissue plasminogen activator was significantly associated with deterioration (hazard ratio 2.25; 95% confidence interval [CI]: 1.13–4.49) even after controlling for the association of deterioration with the early poststroke period. Deterioration conferred an increased risk of poor outcome (modified Rankin Scale scores 3–6) at discharge (relative risk: 1.80; 95% CI: 1.71–1.93). Reversion back to predeterioration deficits occurred in 38% of patients, and was associated with reduced risk of poor outcome at discharge (relative risk: 0.12; 95% CI: 0.02–0.83). Treatment with tissue plasminogen activator conferred better chances of spontaneous recovery to predeterioration deficits after initial deterioration (hazard ratio: 4.36; 95% CI: 1.36–14.01).

Conclusion: More than 40% of patients with SCS deteriorate neurologically. Deterioration tends to occur early after stroke, spontaneously reverses in approximately one-third of cases, and poses an increased risk of poor outcome. Therapies are needed to prevent, arrest, or reverse deterioration in patients with SCS. *Neurology*® 2014;83:398–405

GLOSSARY

CI = confidence interval; HR = hazard ratio; IQR = interquartile range; m-NIHSS = motor component of the NIH Stroke Scale; mRS = modified Rankin Scale; ND = neurologic deterioration; NIHSS = NIH Stroke Scale; SCS = subcortical stroke; tPA = tissue plasminogen activator.

Neurologic deterioration (ND) occurs in 20% to 40% of patients with acute ischemic stroke,^{1–3} and is associated with increased morbidity and mortality.⁴ Various factors associated with ND have been reported.^{5–10} Deterioration and fluctuations are particularly characteristic of subcortical strokes (SCS),^{11,12} and almost one-third of patients with this particular stroke subtype are left dependent.¹³ SCS have also been reported as the most likely cause of ND during the first week after stroke onset, with a proportion of patients undergoing neurologic fluctuation estimated to range between 20% and 70%.¹⁴ Unfortunately, once deterioration has occurred, there are no effective therapies to arrest or reverse it.

Although deterioration and fluctuation are common, there is a lack of prospective data on the natural history and clinical course of neurofluctuation in SCS. The cause of deterioration in these patients is uncertain, with only weak clinical and imaging predictors thus far identified. Before designing a preventive or treatment trial for deterioration, a better understanding of

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the natural history of neurofluctuation in SCS is needed. We conducted a prospective study of patients with SCS to identify how often ND occurs, and with what frequency patients with deterioration recover to their predeterioration neurologic status. In addition, we sought to evaluate whether deterioration was associated with worse outcome. Lastly, we aimed to explore predictors of neurofluctuation in SCS patients.

METHODS Study design. We conducted an observational, prospective study by enrolling and following a predefined cohort of patients with SCS. Patients were identified and enrolled within 24 hours of symptom onset and were followed through the course of hospitalization for ascertainment of incidence of neurofluctuations during an accrual period of 3 years (2008–2011). We also collected poststroke functional status at discharge.

Patient evaluation. At our center, a stroke faculty or fellow evaluates all patients presenting to the emergency department with suspected acute ischemic stroke. Following American Heart Association guidelines, eligible patients presenting within 4.5 hours of symptom onset are treated with IV tissue plasminogen activator (tPA). All stroke patients undergo routine diagnostic studies that include brain CT and/or MRI, vascular imaging using CT or magnetic resonance angiography or ultrasound Doppler study, and an echocardiogram. Patients are admitted to our stroke unit for evaluation, observation, and in-hospital treatment.

Cohort selection. Patients presenting within 24 hours of symptom onset were assessed for clinical and radiologic evidence of SCS. For inclusion, neuroimaging findings had to be consistent with acute subcortical hemispheric or brainstem ischemic stroke in a penetrating vessel territory on MRI or CT. A purely subcortical infarct had to be visualized on diffusion-weighted imaging or by CT hypodensity consistent with an acute or subacute infarct in the territory of the patient's symptoms. All patients were thus included with infarcts in the distribution of the anterior choroidal, lenticulostriate arteries, or perforators of the basilar, posterior cerebral, and posterior communicating arteries. Patients with cardioembolic strokes, cortical signs (visual field cut, aphasia, neglect), or with imaging showing a cortical or cerebellar location were excluded.

Ascertainment of outcome and follow-up. The primary outcome, i.e., ND and reversion back to predeterioration deficits, was measured using the NIH Stroke Scale (NIHSS). For each patient, an NIHSS assessment was performed by a member of the stroke team (faculty or fellow) upon presentation to the emergency department, and subsequently on a daily basis through the period of hospitalization. An additional NIHSS assessment was performed whenever examination deteriorated. Upon notification of deterioration, a stroke team member reassessed the patient and performed the additional NIHSS evaluation. Deterioration in neurologic status was defined as an increase of 1 point or more in the motor portion of any subsequent NIHSS (daily or additional) for assessment of limb movement (0 = no drift, 1 = drift but sustained antigravity, 2 = some effort vs gravity, 3 = no effort vs gravity, 4 = no movement). Patients who deteriorated and then improved to the predeterioration NIHSS status at a later time point during hospitalization both in terms of total NIHSS and the motor subcomponent were regarded to have spontaneously reversed. Each

incident deterioration with or without reversal was recorded for all enrolled patients. A modified Rankin Scale (mRS) score was obtained directly at the time of discharge by a certified stroke team member.

Intracranial stenosis and atherosclerosis. Determination of intracranial stenosis and atherosclerosis was based on the neuro-radiologist interpretation. If middle cerebral artery or basilar stenosis was observed associated with the infarct, it was classified as localized intracranial stenosis. If there was generalized diffuse atherosclerosis without focal stenosis, then it was labeled as diffuse intracranial atherosclerosis.

Hospital treatment. All patients who deteriorated were administered IV fluids, the head of the bed was placed at 0 to 15 degrees depending on risk of aspiration, and emergent brain imaging was performed. The patients were not given IV heparin or loading doses of antiplatelets. Hyperglycemia was treated with sliding-scale insulin to maintain normal blood glucose. Patients continued to receive standard of care regarding blood pressure management, deep venous thrombosis prophylaxis, nursing care, and rehabilitation therapies.

Statistical analysis. Continuous variables are reported as either mean (SD) or median (interquartile range [IQR]). Categorical variables are reported as frequency and percentages. The NIHSS and mRS were dichotomized for certain analyses—NIHSS (mild stroke: ≤ 5 ; moderate to severe stroke: > 5), mRS (good outcome: 0–2; poor outcome: 3–6). Cumulative incidence and incidence rates have been calculated using standard formulae.¹⁵ The Andersen-Gill Cox proportional hazard model was used to account for multiple failure events.¹⁶ Factors with clinical and statistical significance (p value < 0.25 on univariable analysis) were used for model building. Schoenfeld and Cox-Snell residuals were used to test proportionality assumption and overall fit of the final model. Log binomial regression was performed for estimation of risk ratios for poor outcome.^{17–20} All tests were performed at 0.05 level of significance using STATA version 12 (StataCorp, College Station, TX).

Sample-size estimation and power analysis. Previous retrospective studies have reported prevalence of ND to be approximately 50% in patients with small-vessel disease and lacunar strokes.¹¹ Using this estimate, we calculated a minimum sample-size requirement of 85 patients for determining the true incidence rate within $\pm 15\%$ with 95% confidence.²¹

Standard protocol approvals, registrations, and patient consents. Informed consent was obtained from each enrolled patient. The institutional review board of the University of Texas and the ethics committee of Memorial Hermann Hospital at Texas Medical Center in Houston approved the study.

RESULTS Summary. For the 90 patients enrolled in this study, the average duration of in-hospital follow-up was 2.9 days. All enrolled patients completed in-hospital follow-up, and there were no in-patient deaths.

In-hospital ND and associated factors. Based on the defined criteria, 37 patients (41.1%) experienced ND during hospitalization, not attributable to hypotension or hypoglycemia. The median (IQR) time to deterioration from first NIHSS score collected was 17 (3.7–22.9) hours, whereas it was 21 (5.2–41) hours from stroke onset. Furthermore, 75.6% of patients (28/37) deteriorated within 24 hours from the time

Table 1 Univariable analysis of demographic, risk, and clinical factors for patients with and without deterioration

	All patients (n = 90)	Patients with deterioration (n = 37)	Patients without deterioration (n = 53)	Hazard ratio (95% CI)	p Value
Age, y, mean $\pm$ SD	62.5 $\pm$ 11.5	62.9 $\pm$ 11.6	62.3 $\pm$ 11.5	1.00 (0.98–1.02)	0.85
Males, n (%)	48 (53.3)	19 (51.4)	29 (54.7)	0.88 (0.47–1.63)	0.69
Ethnicity, n (%)					
White (non-Hispanic)	40 (44.4)	17 (45.9)	23 (43.4)	Referent category	
Black	36 (40.0)	14 (37.8)	22 (41.5)	0.70 (0.36–1.35)	0.29
Hispanic	11 (12.2)	5 (13.5)	6 (11.3)	1.04 (0.41–2.61)	0.94
Other	3 (3.3)	1 (2.7)	2 (3.7)	0.59 (0.09–3.38)	0.54
Risk factors, n (%)					
Hypertension	68 (75.6)	28 (75.7)	40 (75.5)	0.89 (0.44–1.83)	0.76
Diabetes mellitus	28 (31.1)	13 (35.1)	15 (28.3)	1.21 (0.63–2.32)	0.58
Coronary artery disease	6 (6.7)	2 (5.4)	4 (7.5)	0.60 (0.19–1.83)	0.37
Hyperlipidemia	27 (30.0)	11 (29.7)	16 (30.2)	0.93 (0.49–1.80)	0.84
Smoking	37 (41.1)	16 (43.2)	21 (39.6)	0.87 (0.48–1.58)	0.64
Baseline NIHSS score, median (IQR)	4 (2–7)	4 (2–6)	4 (2–7)	0.91 (0.83–1.00)	0.06
Baseline NIHSS score <5, n (%)	55 (61.1)	25 (67.6)	30 (56.6)	1.57 (0.81–3.05)	0.18
Infarct location, n (%)					
Thalamus	22 (24.4)	10 (27.0)	12 (22.6)	Referent category	
Basal ganglia	21 (23.3)	6 (16.2)	15 (28.3)	0.71 (0.26–1.94)	0.50
Internal capsule	19 (21.1)	7 (18.9)	12 (22.6)	0.78 (0.32–1.91)	0.59
Pontine infarct	14 (15.6)	8 (21.6)	6 (11.3)	1.30 (0.57–2.99)	0.53
White matter infarct	7 (7.8)	4 (10.8)	3 (5.7)	1.38 (0.48–3.95)	0.55
Chronic ischemic change	3 (3.3)	1 (2.7)	2 (3.7)	0.61 (0.10–3.72)	0.59
MRI negative or not done	4 (4.4)	1 (2.7)	3 (5.7)	0.56 (0.07–4.22)	0.58
ICS, n (%)					
No ICS	46 (51.1)	22 (59.5)	24 (45.3)	Referent category	
Localized ICS	17 (18.9)	8 (21.6)	9 (16.9)	1.04 (0.48–2.25)	0.92
Diffuse ICS	27 (30.0)	7 (18.9)	20 (37.7)	0.59 (0.25–1.38)	0.22
ICS vascular territory, n (%)					
Right MCA	3 (3.3)	3 (8.1)	0 (0.0)		
Left MCA	2 (2.2)	0 (0.0)	2 (3.8)		
Bilateral MCA	4 (4.4)	1 (2.7)	3 (5.7)		
Right PCA	2 (2.2)	1 (2.7)	1 (1.9)		
Left PCA	1 (1.1)	1 (2.7)	0 (0.0)		
Basilar artery	3 (3.3)	2 (5.4)	1 (1.9)		
Vertebral artery	2 (2.2)	0 (0.0)	2 (3.8)		
tPA administered, n (%)	28 (31.1)	18 (48.7)	10 (18.9)	3.20 (1.77–5.77)	<0.01
Onset to first observation time, h, median (IQR)	5.2 (2.4–13.0)	2.8 (1.7–6.4)	8.5 (4.1–15.3)	5.7 (1.35–7.16)	<0.01
Onset to first observation time <6 h, n (%)	47 (52.2)	27 (72.9)	20 (37.7)	3.16 (1.62–6.18)	0.001

Abbreviations: CI = confidence interval; ICS = intracranial stenosis; IQR = interquartile range; MCA = middle cerebral artery; NIHSS = NIH Stroke Scale; PCA = posterior cerebral artery; tPA = tissue plasminogen activator.

point when the first NIHSS was measured. The median (IQR) increase in total NIHSS score was 3 (2–5) at the time of deterioration. Fourteen of 37

patients (37.8%) spontaneously reversed back to pre-deterioration deficits, among whom 2 patients had a subsequent episode of deterioration without reversal.

Figure 1 Kaplan-Meier estimates for time to deterioration in patients with and without IV tPA treatment

Hazard ratio and 95% CI are reported for tPA-treated and nontreated groups, controlling for onset to time of treatment and baseline stroke severity. Time zero represents the first NIH Stroke Scale assessment time point, following which patients were enrolled in the cohort. CI = confidence interval; tPA = tissue plasminogen activator.

The cumulative incidence of in-hospital ND was 43.3%, and the incidence rate was 2.1 per 10 person-days. Univariable analysis for estimation of hazard ratio (HR) for deterioration is shown in table 1. Patients who received tPA and those with shorter stroke onset to first observation time had a significantly higher risk of ND. In the final multivariable model, tPA administration remained significantly associated with deterioration (HR: 2.25; 95% confidence interval [CI]: 1.13–4.49), after controlling for baseline stroke severity and onset to first NIHSS observation time. The final model did not violate proportionality of hazard assumption ($p = 0.25$). No significant interactions were detected between the covariates. Kaplan-Meier survival curves comparing time to deterioration in patients with and without tPA administration are shown in figure 1.

Factors associated with spontaneous improvement after deterioration. The median (IQR) time for spontaneous reversal to predeterioration deficits was 21 (5.32–26.3) hours. Other than the use of tPA, no demographic or clinical factors showed any significant differences between the patients who did and did not spontaneously reverse (table 2). Patients treated with tPA had a greater probability of returning to predeterioration deficits (HR: 4.36; 95% CI: 1.36–14.01), as demonstrated in figure 2. On multivariable analysis for estimation of HR, none of the other covariates significantly influenced this association. Treatment with tPA was found to be significantly associated with both deterioration and spontaneous return to predeterioration deficits. The proportion of tPA-treated and nontreated patients cycling through the

complete course of deterioration and then return to predeterioration deficits is shown in figure 3.

Clinical and functional outcomes. Patients who deteriorated had a higher risk of poor outcome even after adjusting for age, initial stroke severity, and use of tPA (relative risk: 1.80; 95% CI: 1.71–1.93). Likewise, patients who recovered back to predeterioration deficits had significantly decreased risk of a poor outcome (relative risk: 0.12; 95% CI: 0.02–0.83), relative to those who deteriorated but did not revert to predeterioration deficits.

Association with infarct location or intracranial stenosis. We found no associations between infarct locations or intracranial stenosis and risk of deterioration (table 1).

DISCUSSION In this prospectively observed cohort, approximately 40% of patients with SCS underwent ND, the majority of cases occurring within the first 24 hours of observation. A large proportion (62%) of patients who deteriorated did not recover back to predeterioration deficits. These findings support the high frequency of neurofluctuation reported in prior retrospective studies.^{11,22} Because of the prospective design, we believe our data depict a reliable estimate of the true incidence rate of deterioration and reversal to predeterioration deficits. Our findings suggest that ND in patients with SCS is fairly common and that spontaneous reversal with conservative management occurs only in one-third of these patients.

We found that the probability of ND in patients with SCS is significantly higher in the early poststroke period and in those who are treated with tPA. Despite a greater risk of deterioration after treatment with tPA, patients given tPA were more likely to spontaneously recover back to predeterioration deficits. Therefore, despite early deterioration, the tPA-treated group had an overall better outcome. The majority of patients who had not received tPA and deteriorated after hospital admission did not recover back to their baseline deficits. The explanation for increased fluctuations in tPA-treated patients is uncertain but may reflect dynamic changes in the clot precipitated by the drug's lytic effect, i.e., partial lysis, then reocclusion, and eventual clot dissolution. Baseline NIHSS assessment was the same for tPA-treated and nontreated patients (median NIHSS score 4); thus, stroke severity likely would not have explained the higher rates of deterioration in the tPA-treated group.

Because thrombolysis was administered within 4.5 hours of symptom onset to all eligible patients, the effect of tPA on ND may be confounded by earlier presentation. In fact, time from symptom onset to first observation in this study was significantly longer in the nontreated patients. It is therefore possible that patients not treated with tPA could have deteriorated

Table 2 Factors associated with spontaneous improvement after deterioration

	Patients with improvement (n = 14)	Patients without improvement (n = 23)	Hazard ratio (95% CI)	p Value
Age, y, mean $\pm$ SD	60.6 $\pm$ 10.1	64.7 $\pm$ 12.5	0.97 (0.93-1.02)	0.29
Males, n (%)	9 (64.3)	10 (43.4)	1.65 (0.55-4.95)	0.36
Ethnicity, n (%)				
White (non-Hispanic)	8 (57.1)	9 (39.1)	Referent category	
Black	5 (35.7)	9 (39.1)	0.62 (0.20-1.92)	0.41
Hispanic	1 (7.1)	4 (17.4)	0.36 (0.05-2.94)	0.35
Other	0 (0.0)	1 (4.4)	—	—
Risk factors, n (%)				
Hypertension	11 (78.6)	17 (73.9)	1.02 (0.29-3.69)	0.96
Diabetes mellitus	3 (21.4)	10 (43.5)	0.42 (0.12-1.50)	0.18
Coronary artery disease	2 (14.3)	0 (0.0)	—	—
Hyperlipidemia	5 (35.7)	6 (26.9)	1.42 (0.48-4.25)	0.53
Smoking	8 (57.1)	8 (34.8)	2.05 (0.70-5.98)	0.18
Baseline NIHSS score >5, n (%)	9 (64.3)	16 (69.6)	0.89 (0.29-2.96)	0.84
Infarct location, n (%)				
Thalamus	4 (28.6)	6 (26.1)	Referent category	
Basal ganglia	3 (21.4)	3 (13.0)	1.68 (0.37-7.69)	0.49
Internal capsule	3 (21.4)	4 (17.4)	1.10 (0.25-4.96)	0.89
Pontine infarct	1 (7.1)	7 (30.4)	0.02 (0.02-1.84)	0.16
White matter infarct	1 (7.1)	3 (13.0)	0.56 (0.06-5.05)	0.61
MRI negative or not done	1 (7.1)	0 (0.0)	—	—
ICS, n (%)				
No ICS	9 (64.3)	13 (56.5)	Referent category	
Localized ICS	1 (7.1)	7 (30.4)	0.32 (0.04-2.51)	0.27
Diffuse ICS	4 (28.6)	3 (13.0)	1.57 (0.48-5.12)	0.45
ICS vascular territory, n (%)				
Right MCA	1 (7.1)	2 (8.7)		
Left MCA	0 (0.0)	0 (0.0)		
Bilateral MCA	0 (0.0)	1 (4.3)		
Right PCA	0 (0.0)	1 (4.3)		
Left PCA	0 (0.0)	1 (4.3)		
Basilar artery	0 (0.0)	2 (8.7)		
Vertebral artery	0 (0.0)	0 (0.0)		
tPA administered, n (%)	10 (71.4)	8 (34.8)	4.36 (1.36-14.01)	0.01
Onset to first observation time <6 h, n (%)	12 (85.7)	15 (65.2)	3.12 (0.69-14.0)	0.14

Abbreviations: CI = confidence interval; ICS = intracranial stenosis; MCA = middle cerebral artery; NIHSS = NIH Stroke Scale; PCA = posterior cerebral artery; tPA = tissue plasminogen activator.

before presentation. In our data, the HR for the effect of tPA on deterioration was adjusted by approximately 30% after controlling for onset to first observation time, but it remained statistically significant. The strength of association between deterioration and early presentation also suggests that the early poststroke period is an

independent risk factor for ND in SCS patients, and hence the need for early recognition and intervention. Thrombolysis protocols also require more frequent monitoring of neurologic status and therefore it is also possible that deterioration was detected earlier in the tPA-treated patients because of more frequent assessments.

Figure 2 Kaplan-Meier estimates for time to spontaneous reversal in patients with and without IV tPA treatment

Time zero represents time of deterioration. No factors other than IV tPA were found to be associated with spontaneous reversal. The hazard ratio and 95% CI reported are unadjusted. CI = confidence interval; tPA = tissue plasminogen activator.

Our data also show that even after controlling for age, use of tPA, and severity of the initial stroke, patients who had neurologic worsening were approximately at twice the risk of having a poor functional discharge outcome as compared with those who did not worsen. However, patients who had spontaneous reversal after deterioration had an 88% greater chance of having a good discharge outcome. Our findings are supportive of an association between deterioration and spontaneous reversal with short-term outcomes in patients with SCS, and underscore the importance of prediction, early recognition, and targeted therapies to reverse, halt, or even prevent deterioration in patients with SCS.

Figure 3 Proportion of patients with deterioration and spontaneous reversal with and without IV tissue plasminogen activator (tPA) treatment

IV tPA treatment was found to be associated with both deterioration and spontaneous reversal during the course of in-hospital follow-up. A higher proportion of non-tPA-treated patients did not show reversal after deterioration.

All patients were treated with standard of care for deterioration. They were not given any off-label treatments and were not given full-dose heparin. Various off-label approaches have been tried in the past for stabilizing patients with neurofluctuation, including laying the patient supine, IV hydration, volume expansion, withholding antihypertensives, pressors, initiating anticoagulants, and antiplatelet loading.^{23,24} However, none of these modalities have shown sufficient promise to advance to a randomized clinical trial. Our data suggest that the rate of ND in patients with SCS is high, the proportion of patients achieving spontaneous stabilization is low, and the outcomes of patients experiencing deterioration are poor. Thus, this high-risk subgroup is a potential target for the development of novel therapies and strategies to prevent or arrest deterioration.

The findings from our study need to be interpreted in light of several limitations. First, our functional definition for deterioration was an increase of 1 point or more on the motor component of the NIHSS (m-NIHSS). This definition could have underestimated the incidence of any type of ND in SCS patients. There is no agreed upon, universal definition of neurologic worsening in SCS. We selected this criterion because we believed it to be most appropriate to the SCS subtype, where the most prevalent and concerning feature is worsening hemiparesis, as has been reported by other investigators.¹¹ Our scale was also similar to the one used in a prior report on worsening in pontine stroke patients.²⁵ Furthermore, the m-NIHSS may be sensitive to interrater variability. Per protocol, incident deterioration was only recorded if a stroke fellow or a faculty member confirmed it, giving us relative consistency and interval validity in outcome ascertainment. Although an interrater reliability assessment was not conducted as a part of this study protocol, all members of our stroke team are educated to perform the NIHSS with uniform training and certification. Recent unpublished data from our center show an excellent κ statistic for m-NIHSS (0.75–1). Similar agreement statistics for m-NIHSS have been reported by other centers.^{26–30} Finally, although we defined ND as a greater than 1-point change, 27 of the 37 patients (73%) who deteriorated had a greater than 1-point increase on the m-NIHSS.

A second limitation is that our data do not conclusively rule out non-neurologic causes of deterioration. However, infections (e.g., urinary tract infection and pneumonia) are an unlikely cause as they occurred in a small proportion of the study patients (6.6% and 3.3%, respectively). While blood pressure and glucose control is standardized for tPA and non-tPA patients, it is possible that smaller, although clinically relevant changes in blood pressure and/or glucose may have occurred in the perideterioration period that we cannot adjust for in our analyses.

We also need to point out that we did not collect long-term outcome data and therefore cannot draw conclusions on the effect of deterioration on long-term outcomes. We recognize that this study was single center and hence our ability to generalize our findings to centers with different patient populations and treatment protocols is limited. A multicenter study involving a larger number of patients can also help pursue the hypothesis of differential risks of deterioration for various SCS subtypes. Finally, we note that our study was powered to determine the incidence of neurofluctuation and any subsequent analyses are best interpreted as associative rather than causal.

The results from this study establish a natural history of neurofluctuation in patients with SCS, provide evidence of poor short-term functional outcome associated with deterioration, and underscore the need for testing novel therapies to treat ND in SCS.

AUTHOR CONTRIBUTIONS

F.S.V.: drafting the manuscript, analysis and interpretation of data. W.J.H.: drafting the manuscript, revision of manuscript for intellectual content. I.A.: revision of manuscript for intellectual content. H.H.: design of study, revision of manuscript for intellectual content. H.P. and R.P.: analysis of data. N.R.G.: revision of manuscript for intellectual content. A.D.B.: design of study, revision of manuscript for intellectual content. S.M.-S. and T.-C.W.: revision of manuscript for intellectual content. M.H.R.: analysis and interpretation of data. A.B.B.: analysis of data. J.C.G.: conceptualization of study, interpretation of data, revision of manuscript for intellectual content. S.I.S.: design and conceptualization of study, drafting the manuscript, interpretation of data, revision of the manuscript for intellectual content.

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DISCLOSURE

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