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Encephalopathy only stroke codes (EoSC) do not result in rt-PA treatments

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Background: Isolated mental status changes as a presenting sign (EoSC+), are not uncommon stroke code triggers. As stroke alerts, they still require the same intensive resources be applied. We previously showed that EoSC+ strokes (EoSC+ Stroke+) account for 0.1–0.2% of all codes. Whether these result in thrombolytic treatment (rt-PA), and the characteristics/ risk factor profiles of EoSC+ Stroke+ patients, have not been reported. **Methods:** Retrospective analysis of stroke codes from an IRB approved registry, from 2004 to 2018, was performed. EoSC+ was defined as a NIHSS>0 for Q1a, 1b, or 1c with remaining elements scored 0. Characteristics and risk factors were compared for EoSC+, EoSC–, EoSC+ Stroke+, and rt-PA (EoSC+ Stroke+TPA+) patients. **Results:** EoSC+ occurred in 55/2982 (1.84%) of all stroke codes. EoSC+ Stroke+ occurred in 8/55 (14.5%) of EoSC+ codes and 8/2982 (0.27%) of all stroke codes. 6/8 (75%) of EoSC+ Stroke+ scored NIHSS=1. When comparing EoSC++versus EoSC–, Hispanic ethnicity ($p=0.009$), hypertension ($p=0.02$), and history of stroke/TIA ($p=0.002$) were less common in EoSC+. No demographic/risk factor differences were noted for EoSC+ Stroke+ vs. EoSC+ Stroke–. No cases of rt-PA eligibility/treatment were noted. In EoSC+ Stroke+ analysis, imaging positive stroke/intracranial hemorrhage was noted on only 3 cases (3/2982=0.10% of all stroke codes) and none were posterior stroke. **Conclusions:** EoSC+ rarely results in stroke/TIA (0.27%) or stroke (0.10%), and in our analysis never (0%) resulted in rt-PA. Sub-analysis did not show missed rt-PA or posterior strokes. Understanding characteristics, and knowing that EoSC+ Stroke+ patients are unlikely to receive rt-PA, may help triage stroke resources.

Keywords: stroke—rt-PA—Encephalopathy—Cerebrovascular disease—Stroke alert—Triage—Resource utilization

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Introduction

Inpatient stroke code alert systems and protocols are widely used and have expedited response times and recombinant tissue plasminogen activator (rt-PA) administration in acute stroke. Stroke code systems' effectiveness hinge on rapid administration of multiple resources for each code patient, though 30% of stroke codes are stroke mimics.¹

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Encephalopathy only stroke codes (EoSC+) account for 1.5–2.5% of overall stroke codes and 8–9% of all encephalopathy only stroke codes.² While isolated encephalopathy is typically a stroke mimic, this symptom can very rarely be the presentation of bilateral, basilar or thalamic strokes.

Strokes characterized by isolated encephalopathy without other neurologic findings (EoSC+ Stroke+) account for only 0.1–0.2% of all stroke codes.² Whether this small cohort receives rt-PA or if these cases represent “missed opportunity” of rt-PA is unknown.

In this analysis we evaluate the rate of of rt-PA administration in encephalopathy only stroke codes (EoSC+), and encephalopathy only strokes (EoSC+ Stroke+). We furthermore conduct a clinical case review of their characteristics and risk factors for EoSC+ Stroke+ cases.

Methods

We retrospectively assessed consecutive patients in a prospectively collected, IRB approved, UCSD stroke code

database, from patients seen between June 2004 and June 2018. This database contains demographics, treatment times, and outcome data on all patients in which the institution's stroke code policy was activated.

EoSC+ was defined as any stroke code patient where the stroke code NIHSS individual item scores showed evidence of encephalopathy on the level of consciousness questions (defined as: answers for Question 1a, Question 1b, or Question 1c >0) while the remainder of the NIHSS items scored without deficit (score=0).

Stroke code patients were grouped according to having "Encephalopathy Only" (EoSC+), "not Encephalopathy-Only" (EoSC-), EoSC with final diagnosis of stroke or TIA (EoSC+ Stroke+), no EoSC but final diagnosis of stroke/TIA (EoSC- Stroke+) and rt-PA administration (EoSC+ Stroke+ TPA+). Fig. 1 demonstrates a schematic of these study definitions.

We analyzed baseline characteristics of age, sex, race, initial NIH Stroke Scale (NIHSS), diabetes, hypertension (HTN), coronary artery disease (CAD), atrial fibrillation (afib), history of stroke or TIA, mean systolic blood pressure during code, alcohol, and smoking. We compared these demographics/risk factors for EoSC+, EoSC-, EoSC+ Stroke+, and rt-PA (EoSC+ Stroke+TPA+) patients. Stroke was defined as either acute ischemic stroke, intracerebral hemorrhage or imaging positive, symptom negative (silent cerebral infarction) on discharge ICD coding.

Demographics were compared via chi-squared (nominal), Fischer's exact (nominal), ANOVA/*t*-test (continuous), as appropriate to the data. Correlation with Spearman (nominal) or Pearson's (continuous) was performed as appropriate. A *p*-value of <0.05 was considered significant.

Results

A total of 2982 stroke codes were identified. EoSC+ accounted for 55/2982 (1.84%) of stroke codes, and 8/55 (14.5%) of EoSC+ patients had a final diagnosis of stroke

(EoSC+ Stroke+). EoSC+ Stroke+ accounted for 8/2982 (0.27%) of all stroke codes (Fig. 1).

No EoSC+ case was given rt-PA. Accordingly, EoSC+ TPA+ and EoSC+ Stroke+TPA+ were 0/55 (0%) and 0/8 respectively (0%). On review none of these cases were rt-PA eligible (<3–4.5 h onset, no clinical contraindications).

When comparing demographics/risk factors of EoSC+ and EoSC-, Hispanic ethnicity ($p=0.009$), HTN ($p=0.02$), and history of stroke/TIA ($p=0.002$) were more common in the EoSC- cohort. No statistically significant demographic/risk factor differences were noted for EoSC+ Stroke+ vs. EoSC- Stroke+ or EoSC+ Stroke+ vs. EoSC+ Stroke- (Table 1).

In the EoSC+ Stroke+ analysis, the NIHSS mode, median, range was 1, 1, 1–4 respectively and 6/8 (75%) of EoSC+ Stroke+ scored a NIHSS of 1. Imaging positive middle cerebral artery stroke [2/3] and intracranial hemorrhage [1/3] was noted in only 3/8 (37.5%) of EoSC+ Stroke+ cases, of which none qualified for rt-PA. True stroke therefore represented 3/2982 (0.001%) of all stroke codes. None of these strokes were posterior stroke. The remaining 5/8 of EoSC+ STROKE+ represented transient neurologic events that on clinical review were considered "possible TIA". Table 2 details the clinical scenarios and radiographic correlates within the EoSC+ Stroke+ group.

Discussion

To our knowledge this is the first study to show encephalopathy only stroke codes do not receive rt-PA. This data is useful in triaging in stroke alerts, especially when hospital resources are strained. This is particularly relevant in light of the recent Coronavirus-2019 (COVID-19) pandemic which has forced the healthcare systems, and according hyper acute stroke management, to be more prudent in personnel and resource deployment.³ This study adds to the growing question of how can we improve the specificity of our intrinsically high sensitive stroke alert systems.²

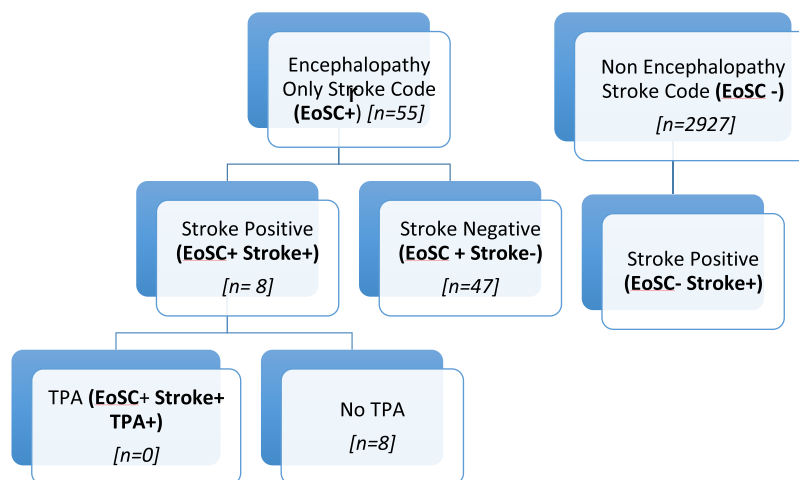


Fig. 1. EoSC study definitions.

Table 1. Demographics table of EoSC+ Stroke+ vs. EoSC – Stroke+ (Top) and EoSC + Stroke+ vs. EoSC + Stroke– (Bottom).
There was no statically differences in demographic/risk factors between groups. Represented as raw value (percentage).

	EoSC+ Stroke+ (n = 8)	EoSC– Stroke+ (n = 2974)	p Value
Age (y)	68	76	0.12
Gender			
<i>Male</i>	1 (20)	444 (58)	
<i>Female</i>	4 (80)	317 (42)	
Race			
<i>Asian</i>	4 (80)	48 (6.3)	0.39
<i>Black</i>	1 (20)	72 (9.5)	
<i>Native American</i>	0	1 (.1)	
<i>Pacific Islander</i>	0	10 (1.3)	
<i>White</i>	0	62 (82%)	
Coronary Artery Disease	1 (20)	177 (23)	1
Diabetes	3 (60)	188 (24)	0.16
Hypertension	4 (80)	529 (70)	1
Atrial fibrillation	1 (2)	192 (25)	1
History of stroke or TIA	2 (40)	248 (32)	0.66
Mean systolic	154	148	0.53
Smoking history	0 (0)	172 (13)	0.61
	EoSC+ Stroke+ (n = 8)	EoSC+ Stroke– (n = 47)	p Value
Age (y)	76	67	0.19
Gender			
<i>Male</i>	3 (38)	20 (42)	1
<i>Female</i>	5 (62)	27 (58)	
Race			
<i>Asian</i>	2 (25)	2 (4)	0.11
<i>Black</i>	1 (37)	3 (7)	
<i>Native American</i>	0	0	
<i>Pacific Islander</i>	0	0	
<i>White</i>	5 (62)	38 (88)	
Coronary artery disease	2 (25)	6 (75)	0.66
Diabetes	4 (50)	8 (17)	0.06
Hypertension	5 (62)	19 (40)	0.28
Atrial fibrillation	2 (25)	5 (10)	0.27
History of stroke or TIA	3 (37)	5 (10)	0.08
Mean systolic	143	135	0.17
Smoking history	0 (0)	4 (8.5)	1

Similar to our past study², eventual stroke accounted for only 8/55 (14.5%) of EoSC+ and 8/2982 (0.27%) of all stroke codes of cases. Reassuringly, there were no missed rt-PA opportunity for either cohort. This may represent the patient population or our institutional practices. The lack of rt-PA administration is consistent with past findings that show stroke mimics account for a small population of rt-PA administration.⁴ Notably mimics that get rt-PA have low rates of symptomatic ICH, which has lead some to argue that there are few clinical repercussions to undifferentiated mimics.⁵ With increasing spoke-hub stroke models, and complexity of regional stroke care, our findings are still important in the context of hospital triage, allocation and hospital workflow.

The majority of strokes in the EoSC+ population had low NIHSS scores, the majority scoring a 1. While a TIA

or transient neurologic mimic may explain this, it is striking that a middle cerebral artery infarction and cerebral hemorrhage were in this group. This could be an evolving clinical presentation, variability in NIHSS among providers, or a limitation of the strict NIHSS definition used. This poses if using a more liberal NIHSS definition to include other non localizing NIHSS features that accompany encephalopathy such as bilateral weakness, or muteness², may yield a more comprehensive spectrum of EoSC+.

Our study suggest the EoSC is a clinically challenging group that needs to be further studied. There were no demographic or vascular risk factors to differentiate EoSC + Stroke+ from EoSC + Stroke –. Moreover there were no posterior strokes or symptoms in the EoSC+ Stroke+ group. Two EoSC + Stroke+ patients on chart

Table 2. Case descriptions and MRI findings of EoSC + Stroke + Cohort. SAH = Subarachnoid hemorrhage. MCA = Middle cerebral artery.

Diagnosis	Reason for stroke alert	Neuroanatomic findings on MRI
SAH	Encephalopathy following traumatic motor vehicle accident	Left small curvilinear inferior temporal SAH. Left large superior parietal infarct
MCA stroke	Encephalopathy with possible sensory changes	Right moderate centrum ovale, corona radiata, internal capsule infarcts. Right punctate superior frontal gyrus infarct
MCA stroke	Dizziness, palpitations and subjective slurring	Left punctate corona radiate infarct
Possible TIA	Subjective recurrent slurred speech	None
Possible TIA	Bilateral arm weakness, sleepiness	None
Possible TIA	Lethargy, left leg weakness	None
Possible TIA	Generalized fatigue	None
Possible TIA	Encephalopathy	None

analysis showed radiographic findings of sizable unilateral right (subcortical) or left (cortical) MCA distribution strokes with locations in the frontal and parietal lobe respectively. The large infarct size with frontal or parietal involvement could explain isolated encephalopathy. No EoSC+ Stroke + case showed clear neuroanatomical correlate to the following neurologic localizations for encephalopathy: midbrain, medial/bithalamus, or large bicortical. Thus *a priori* determination of Stroke+ vs. Stroke– in the EoSC cohort is not possible based on these findings. This may argue for a comprehensive neurologic exam, and rapid magnetic resonance imaging for this population, both resource intense. How institutions will weigh this clinically difficult cohort against a rare probability of stroke that lends itself to resource optimization is yet to be determined.

Limitations of this study include the use of a retrospective database and dependence on accurate documentation of NIHSS and clinical presentation. This study reflects the findings at a Southern California metropolitan primary stroke center at a tertiary academic hospital, and may not be generalizable to other settings. Finally, this study has a lower number of isolated encephalopathy codes compared to past studies.⁶ This may be reflective of the strict NIHSS criteria utilized, and the NIHSS by nature does not capture the many intangible features of encephalopathy clinical exams. A key limitation to generalizing the use of these results would be the “lost chance standard” in rt-PA.⁷

Overall our study showed that isolated encephalopathy stroke codes account for a low rate of eventual stroke diagnosis, no administration of rt-PA and no clinically

“missed opportunities” for rt-PA. Future studies will expand this investigation with a broader definition of EoSC and prospectively implementation of isolated encephalopathy as a triage criteria in stroke alerts.

Declaration of Competing Interest

The authors have no financial disclosures to declare and no other conflicts of interest/disclosures to report

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