Conjugate Eye Deviation on CT Associated With Worse Outcomes Despite IV Thrombolysis

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Abstract

Introduction: Rapid stroke management has significant implications in patient outcomes. Ipsilateral computed tomography conjugate eye deviation (CT-CED) has been associated with worse outcomes but has never been evaluated as predictive of vascular occlusion. To test the hypothesis that CT-CED is a marker for vascular occlusion, we evaluated patients treated with intravenous tissue plasminogen activator (IV tPA). **Methods:** We performed a retrospective analysis of patients with acute ischemic stroke treated with IV tPA at a large tertiary care hospital over an 18-month period. A waiver of informed consent was granted. Two examiners evaluated baseline brain CTs blinded to the location of infarct to assess the presence of CT-CED and follow-up imaging for the location of infarct and the presence of intracranial large vessel occlusion. Demographics, initial National Institutes of Health Stroke Scale (NIHSS), modified Rankin Scales (mRSs), and hospital length of stay (LOS) were collected. **Results:** Among 104 patients treated with IV tPA, 36 had CT-CED. Inter-rater reliability for CT-CED was excellent ($\kappa = 0.97$; 95% confidence interval: 0.98-1.0). The CT-CED group was older (69.8 vs 64 years; $P = .038$), had higher initial NIHSS (14.6 vs 11; $P = .01$), worse mRS (3.2 vs 2.4; $P = .03$), and longer LOS (8.4 vs 6.4; $P = .05$) compared with those without CT-CED. A vascular occlusion in the territory of the infarct was seen in 58% of patients with CT-CED versus 32% without CT-CED ($P < .01$). Atrial fibrillation (AF) was diagnosed in 61% patients with CT-CED versus 22% without ($P < .01$). **Conclusion:** The CT-CED is associated with higher initial NIHSS, large vessel occlusion, and AF. Prospective studies are needed to ascertain whether CT-CED may be utilized part of a screen for endovascular therapy.

Keywords

stroke, acute, deviation, gaze, management, conjugate eye deviation, frontal eye field, spatial neglect

Rapidity of stroke treatment correlates with better outcomes.¹ However, the lack of experienced examiners in various settings and the possibility of ambulance-based computed tomography (CT) before neurological assessment highlight the need to quickly identify potential endovascular candidates.² Conjugate eye deviation (CED) can localize to multiple areas including the medial frontal gyrus, the parafornix reticular formation, and other cortical areas involved in spatial neglect,³⁻⁵ and may be associated with other acute neurological events such as seizure, postictal states, and systemic mimics of stroke such as hyperglycemia.⁶⁻⁸ Ipsilateral CED on brain CT (CT-CED) has been associated with worse outcomes in patients with stroke⁹ but has not been evaluated as a tool in identifying acute endovascular therapy candidates. The CED suggests cortical frontal lobe involvement in most cases and may indicate large vessel occlusion. As it is readily detected on CT, it is an attractive potential biomarker to identify large vessel occlusion. Given the advent of mobile stroke

units with noncontrast CT capability, telestroke in facilities without angiographic capability, as well as new guidelines for intervention with level I evidence, the ability to triage patients to interventional capable centers will become more important. To test the hypothesis that CED is a marker for vascular occlusion, we performed a retrospective analysis of patients treated with thrombolytics (intravenous tissue plasminogen activator [IV tPA]).

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Table 1. Demographic, Clinical, and Radiographic Information.

	Total (N = 104)	CT-CED (n = 36)	Non CT-CED (n = 68)	P Value
Age (mean $\pm$ SD), years	66.4 $\pm$ 12.8	69.8 $\pm$ 12.3	64 $\pm$ 12.7	.05
Gender (male, %)	57 (54%)	17 (47%)	40 (58%)	.87
Race-ethnicity				
White	20 (19%)	9 (25%)	11 (16%)	.13
Black	41 (39%)	15 (42%)	26 (38%)	.97
Hispanic	43 (41%)	12 (33%)	31 (45%)	.88
Initial NIHSS	12.2 $\pm$ 7.1	14.6 $\pm$ 6.5	11.8 $\pm$ 9.8	.01
NIHSS subscore gaze preference (1)	19	10 (27%)	9 (13%)	.03
NIHSS subscore gaze deviation (2)	18	10 (27%)	8 (11%)	.02
Atrial fibrillation	36 (%)	22 (61%)	15 (22%)	.01
EF	50 $\pm$ 12.6	49 $\pm$ 14.4	51 $\pm$ 11.5	.5
HTN history	69 (66%)	22 (61%)	47 (70%)	.79
A1C	6 $\pm$ 1.3	6.1 $\pm$ 0.8	6.0 $\pm$ 1.5	.73
LDL	96.8 $\pm$ 41	86 $\pm$ 35	102 $\pm$ 43	.98
HDL	48 $\pm$ 19.6	48 $\pm$ 23	48 $\pm$ 18	.95
Large artery occlusion	42	21 (58%)	21 (30%)	.01
Cortical involvement on follow-up imaging	59	28 (77%)	31 (28%)	.01
mRS	2.7 $\pm$ 1.8	3.2 $\pm$ 1.7	2.4 $\pm$ 1.9	.03
LOS	7.1 $\pm$ 4.5	8.4 $\pm$ 4.2	6.4 $\pm$ 4.5	.05

Abbreviations: A1C, Hemoglobin A1c; ACA, Anterior Cerebral Artery; CT-CED, computed tomography conjugate eye deviation; EF, Ejection Fraction; HDL, High Density Lipid; HTN, Hypertension; ICA, Internal Carotid Artery; LDL, Low Density Lipid; LOS, length of stay; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; PCA, Posterior Cerebral Artery; SD, standard deviation.

Methods

In a retrospective, observational, single tertiary care institutional review board-approved registry of hospital-based patients, we evaluated consecutive patients receiving in-hospital IV tPA over an 18-month period from January 2013 to May 2014. Two examiners (N.H.S. and N.B.) independently evaluated initial CTs blinded to clinical data or subsequent imaging for the presence of CED, defined as conjugate deviation of the lens to either right or left side regardless of the degree of deviation. The territory of the infarct and the presence of large artery occlusion were evaluated on subsequent imaging routinely obtained. Follow-up imaging included magnetic resonance imaging and magnetic resonance angiography or CT and CT angiogram. The arterial distribution of the infarct was correlated with the presence of CT-CED. Age, sex, race-ethnicity, initial National Institutes of Health Stroke Scale (NIHSS), presence of clinical gaze deviation on the baseline neurologic examination and NIHSS subscore, endovascular recanalization after IV tPA, modified Rankin Scales (mRSs) at discharge, and hospital length of stay (LOS) were collected through chart review by investigators (A.T., D.C., and P.K.) blinded to CT-CED assessments. The LOS was evaluated by excluding patients with stays greater than 21 days unrelated to acute management.

Results

The demographic, clinical, and radiographic characteristics of the study population are summarized in Table 1. A total of 104 patients were analyzed, of which 36 had CT-CED designated

Table 2. Location of Large Artery Occlusion.

	CT-CED	Non-CT-CED
Total	21	21
Laterality (left, right, bilateral)	12L, 9R, 0B	11L, 7R, 3B
MCA (M1/M2)	18	13
ACA	0	2
PCA	1	1
Basilar	0	3
ICA	2	2

Abbreviations: CT-CED, computed tomography conjugate eye deviation; MCA, middle cerebral artery.

by at least 1 evaluator. Inter-rater reliability was excellent, with only 1 case of initial disagreement on the presence of CT-CED ($\kappa = 0.97$; 95% confidence interval [CI]: 0.98-1.0). The comparison between clinical gaze deviation on the NIHSS subscore and CT-CED was fair ($\kappa = 0.34$; 95% CI: 0.169-0.5). The CT-CED group was older (69.8 vs 64 years; $P = .038$), had higher initial NIHSS (14.6 vs 11; $P = .01$), worse mRS at discharge (3.2 vs 2.4; $P = .03$), and longer LOS (8.4 vs 6.4; $P = .05$). Atrial fibrillation (AF) was diagnosed in 22 (61%) of 36 with CT-CED and 15 (22%) of 68 without CT-CED ($P < .01$). Cortical involvement on follow-up imaging was seen more frequently in CT-CED (28 [78%] of 36 vs 31 [46%] of 68; $P < .01$). Infarct location was correlated with side of CT-CED in 33 of 36 cases. Table 2 shows the location of large artery occlusions seen of vascular imaging. Sensitivity and specificity of CT-CED for vascular occlusion were moderate 50% (95% CI: 34.2-66) and good 75.6% (95% CI: 62-86), respectively. Positive likelihood ratio of CT-CED for

vascular occlusion was 2.1 (95% CI: 1.2-3.6). Negative likelihood ratio of CT-CED for vascular occlusion was 0.66 (95% CI: 0.47-0.92). These correlated more often with target lesion in patients with CED (21 [58%] of 36 vs 22 [32%] of 68; $P < .01$). The CT-CED was present in 14 (47%) of 30 patients who went to endovascular acute recanalization therapy due to persistent large vessel occlusion after IV tPA.

Discussion

Since the initial observation of the gaze deviation in stroke by Prevost in 1865¹⁰ and localization of the frontal eye field to medial frontal cortex in Brodmann areas 6 and 8,⁵ the potential implications of CED in acute management have been understudied.

The CED is common in stroke. Singer and colleagues reported CED recorded in the NIHSS subscore in 33% of 116 patients with ischemic stroke.¹¹ Similarly, a retrospective study of patients who arrived to the emergency department with a suspected acute stroke demonstrated that 31% of all patients had CT-CED, and 51% of those patients had an ischemic stroke.⁷ Another report evaluated patients in the emergency department and found CT-CED in 14% of nonstroke patients, 36% of patients treated with IV tPA, and 50% of patients with ischemic stroke referred for endovascular recanalization therapy.⁹ Our data demonstrate that approximately 47% of patients treated with IV tPA and endovascular therapy had CT-CED. Our data are the first to demonstrate a moderate sensitivity and a good specificity for vascular occlusion.

Previous studies used angle deviation calculations to calculate CT-CED, which requires rater experience and technical analysis.^{10,12} In this study, we used visual inspection to ascertain CT-CED and found excellent inter-rater reliability; this simple paradigm could be applied in the prehospital setting. These data indicate that CT-CED may be a useful biomarker for future study, trigger advanced evaluation for endovascular therapy in the correct clinical context.

To our knowledge, this is the first study of patients using subjective CT-CED assessments stroke patients receiving thrombolytic therapy and correlating it with endovascular eligibility, such as the case illustrated in Figure 1. Our data demonstrate that CT-CED is associated with higher initial NIHSS, more large artery occlusion, more AF, longer LOS, and worse mRS. Vascular occlusions were predominantly in the anterior circulation with similar frequency in the right and left hemispheres in the CT-CED group, contrary to prior reports suggesting that CED was more common in right hemispheric strokes attributable to visual-spatial deficits.^{11,13}

The AF and cortical involvement of stroke were also significantly associated with CT-CED. These data corroborate the hypothesis that CT-CED may be a marker of cardioembolic stroke. Therefore, the presence of CT-CED in cryptogenic stroke should trigger evaluation with prolonged electrocardiographic monitoring to evaluate for paroxysmal AF.^{14,15}

Three patients had a CT-CED opposite to the side of stroke, including 1 with bilateral infarcts in the right anterior cerebral

Figure 1. Computed tomography conjugate eye deviation (CT-CED) and stroke imaging correlates. A, Noncontrast head CT showing left eye gaze deviation. B, Diffusion-weighted image (DWI) showing restriction in left MCA distribution. C, Cerebral angiogram showing occlusion of proximal left MCA. D, Flow restoration in the left MCA distribution after thrombectomy.

and left middle cerebral arteries (MCA), another with a right occipitotemporal infarct, and a third presenting with a left temporoparietal infarct and generalized seizures. All of these have neuroanatomical correlates, as seizures may cause contralateral gaze deviation and right temporoparietal damage may result in gaze deviation due to spatial neglect.⁵ Although these patients did not correlate with ipsilateral MCA occlusion, aggressive management was still warranted.

Although CT-CED alone may not represent a marker of vascular occlusion given only moderate sensitivity, its combination with other hyperacute signs of stroke and a hyperacute screen may be an approach for future consideration. The hyperdense MCA sign is similar, in that it is between 30% and 50% sensitive with high specificity for vascular occlusion.^{16,17} Current guidelines do not require vascular imaging and this allows for primary stroke centers to directly triage to comprehensive stroke centers with angiographic capabilities after hemorrhage has been ruled out. Current prehospital stroke scales vary and can miss up to 30% of strokes in the field.¹⁸ As systems stroke care centralize inclusion of CT-based approaches in conjunction with clinical scales needs further study.

Limitations of our study include its retrospective design and the use of a single-center study. Inter-rater reliability between NIHSS and CT-CED was not controlled, as patients were not clinically evaluated for primary gaze while in CT. This study's strengths include CT assessment blinding to infarct location and clinical information as well as the design

focusing on correlates of the neurological examination, which can be used in future prehospital studies.

Conclusion

The CT-CED in the correct clinical context may be a viable prehospital biomarker of acute, large vessel stroke with cortical involvement and may aid in prehospital and hyperacute evaluation and management. The CT-CED was associated with higher initial NIHSS, large vessel occlusion, and AF. Prospective studies are needed to ascertain whether CT-CED may be utilized in emergency transport decisions and endovascular therapy evaluation.

Authors' Note

Dr. Shah contributed in drafting and revising the manuscript for content, analysis and interpretation of data, clinical evaluation and management, and concept and design. Dr. Bhatt and Dr. Condes contributed in drafting and revising the manuscript for content and analysis, or interpretation of data. Dr. Tipirneni contributed in drafting and revising the manuscript for content, analysis or interpretation of data, and clinical evaluation and management. Dr. Khandelwal contributed in drafting and revising the manuscript for content, analysis and interpretation of data, and clinical evaluation and management. Dr. Romano contributed in drafting and revising the manuscript for content, analysis and interpretation of data, clinical evaluation and management, concept and design, and study supervision.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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