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Pre-stroke dementia is associated with poor outcomes after reperfusion therapy among elderly stroke patients

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Abstract

Background—In elderly acute stroke patients, reperfusion therapy is often withheld. We sought to determine whether pre-stroke dementia contributed to poor outcomes after reperfusion therapy in these patients.

Methods—All consecutive patients ≥ 80 years who received IV or intra-arterial reperfusion therapy (IAT) were identified in our GWTG-S database. Vascular risk factors, presence of dementia, and outcomes were abstracted from the medical record. Dementia was recorded when listed in past history or when under medical treatment. Primary outcome was in-hospital mortality. Secondary outcome was discharge destination, "favorable" (home, rehabilitation facility) versus "unfavorable" (skilled nursing facility, hospice, death). Multivariate logistic regression models were used to assess outcomes.

Results—Of 153 patients, 72% received IV tPA, 35% IAT, and 7% both. Mean age was 85.8 ± 4.6 years; 13.6% had pre-stroke dementia. In-hospital mortality rate was 35%. The likelihood of death increased with NIHSS (OR 1.14, 95%CI 1.07–1.21), IAT (OR 3.43, 95%CI 1.70–6.92) and dementia (OR 3.61, 95%CI 1.39–9.37), and decreased with IV tPA (OR 0.34, 95%CI 0.17–0.71). Increasing NIHSS (OR 0.90, 95%CI 0.85–0.95), symptomatic intracranial hemorrhage (OR 0.08, 95%CI 0.01–0.67), IAT (OR 0.43, 95%CI 0.22–0.84), and dementia (OR 0.37, 95%CI 0.14–0.97) decreased the likelihood of favorable discharge. In multivariate analysis, only NIHSS (OR 1.13, 95%CI 1.06–1.22) and dementia (OR 5.64, 95%CI 1.88–16.89) independently predicted death and unfavorable discharge destination.

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Dr. Natalia Rost has nothing to disclose.

Conclusions—Among the elderly, pre-stroke dementia is a powerful independent predictor of in-hospital mortality after acute reperfusion therapy for stroke. Future investigations of thrombolysis outcomes in the elderly are warranted.

Key terms

acute stroke; reperfusion therapy; tPA; dementia; outcome

Background

Individuals aged 85 years and older are the fastest growing segment of the geriatric American population [1]. Thus, according to projections, 37% of ischemic stroke patients in the future will be above the age of 84 years [2].

The treatment of elderly patients with acute ischemic stroke (AIS) presents an increasing challenge to physicians. Although age is a known important risk factor for stroke, most pivotal trials of intravenous tissue plasminogen activator (IV tPA) in stroke excluded or underrepresented patients over 80 years [3–5]. Furthermore, no clear criteria exist for patient selection for intra-arterial therapy (IAT), a widely used reperfusion approach that is insufficiently studied for efficacy and outcomes in the elderly [6].

In a pooled analysis of ATLANTIS, NINDS, ECASS, and in several other studies, age was identified as independent predictor of intracranial hemorrhage (ICH) [7, 8]; however, a comparable rate of ICH in younger and older patients was demonstrated by others [9, 10]. While patients older than 85 years were excluded from PROACT II, they were eligible for IAT in MERCI and Multi MERCI[11, 12] albeit underrepresented, with the majority of patients treated being younger than 80 years.

In the absence of clear recommendations for treatment of the elderly with AIS, reperfusion therapy is often withheld. However, overall stroke severity is increased in the elderly population and independently affects stroke outcomes[13]. With or without acute stroke treatment, poor outcomes are more common in older patients[14], and particularly older patients may have significant gain from thrombolytic therapy.

Given the growing elderly population, physicians will have an increasing opportunity to offer reperfusion therapies to older patients. Clarification of clinical factors associated with outcome in elderly patients treated with reperfusion therapy can assist in identifying who will likely benefit from these treatments.

In this study, we sought to determine whether pre-stroke dementia contributed to poor outcomes in stroke patients greater than 80 years old who underwent IV and/or IA reperfusion therapy.

Methods

We retrospectively identified all AIS patients of age 80 and older who received IV or IAT in our institutional prospective Get With the Guidelines Stroke (GWTG-S) database from 2/02-12/09. All aspects of this study were approved by the local Institutional Review Board.

At our institution, IV tPA is administered to all appropriately selected AIS patients based on the current thrombolysis guidelines and regardless of age. The thrombolysis guideline with regard to the blood pressure parameters (systolic blood pressure <185mm Hg and diastolic blood pressure <110mm Hg) were upheld for each subject considered for reperfusion therapy. All AIS patients are considered for IAT based on the institutional protocol if they

present with an NIHSS ≥8, evidence of a proximal vessel cut off on CT or MR angiogram, infarct size <1/3 territory (or <100cc on acute neuroimaging, DWI MRI or head CT), and if they can be treated within 8 hours of last seen well time. The institutional protocol does not contain an age cut-off; however, the final decision to proceed with IAT does require family consent.

Vascular risk factors, symptomatic ICH (sICH), and discharge destination were abstracted from the medical record, using GWTG-S definitions [15]. Diagnosis of dementia was defined as either (1) history of dementia based on report or available medical records, and/or (2) evidence of medical treatment specific for cognitive impairment/dementia. The primary outcome was in-hospital mortality. The secondary outcome was discharge destination dichotomized into “favorable discharge” to home or rehabilitation facility (if the subject was deemed to have “rehabilitation potential” by the multi-disciplinary stroke rehab assessment team) vs. “unfavorable discharge” based on evidence of no rehabilitation potential (including discharge to skilled nursing facility, hospice, or death). Symptomatic intracranial hemorrhage (sICH) was defined as clinical deterioration with evidence of new symptomatic hemorrhagic transformation or ICH on the head CT or brain MRI following reperfusion therapy for AIS. Asymptomatic hemorrhagic transformation cases were not included in this analysis.

Univariate comparisons using Fisher’s Exact test for dichotomous variables, t-test for normally distributed continuous variables, or Wilcoxon rank sum test for ordered categorical variables were used as appropriate. Multivariate logistic regression analysis of outcome included those variables that reached $p<0.2$ in univariate analysis. The level of significance was set $P<0.05$ (two-sided) for all statistical analyses. All statistical analyses were performed using SAS version 9.2 *(SAS Institute, Cary, NC)*.

Results

We identified 153 patients with AIS aged 80 years and older who received acute reperfusion therapy between 02/2002 and 12/2009. Of these, 72% received IV tPA (n=110), 35% IAT (n=54), and 7% both (n=11). Baseline clinical data and demographics of the cohort are summarized in Table 1. Mean age was 85.8 ± 4.6 years (range 80–103), 30.7% were men, 88.2% were white, 98.3% were ambulatory prior to admission, and 10 lived in a nursing home prior to admission Twenty-one patients (13.7%) had a diagnosis of pre-stroke dementia. Of those, 5 (23.8%) were nursing home residents prior to admission, as compared to 5 (3.8%) in the non-demented subjects in this study. The median NIHSS score on admission was 16 (IQR 11–20).

The overall rate of sICH was 6.5% (10/153) with treatment specific rates of 5.5% (IV tPA alone), 3.7% (IAT alone), and 18.2% (combined IV/IAT). Of the 21 patients with pre-stroke dementia, 3 (14.2%) had sICH. Of note, there were two more subjects with dementia who had asymptomatic ICH on routine 24-hour head CT following reperfusion therapy. Two of the three sICH in patients with dementia occurred in areas other than the acute stroke territory.

The in-hospital mortality rate was 35% (54/153 patients), of whom 57% had received IV tPA, 54% IAT, and 11% both. Favorable discharge was recorded for 83/153 (54.3%) patients. Among these patients, 64 (77%) had received IV tPA, 22 (27%) had received IAT, and three (3.6%) had received both. Unfavorable discharge was recorded in 70/153 (45.8%) patients. Of these, 40 (57%) had been treated with IV tPA, 38 (54%) with IAT, and 8 (11%) with both.

In univariate analysis (Table 2, model 1), the odds of in-hospital mortality increased with increasing NIHSS (OR 1.14 per point, 95%CI 1.07–1.21), IAT (OR 3.43, 95%CI 1.70–6.92), and dementia (OR 3.61, 95%CI 1.39–9.37). When treated with IV tPA, the likelihood for death decreased (OR 0.34, 95%CI 0.17–0.71). The odds of favorable discharge (Table 3, model 1) decreased with admission NIHSS (OR 0.90 per point, 95%CI 0.85–0.95), and pre-stroke dementia (OR 0.37, 95%CI 0.14–0.97). Patients who received IAT (OR 0.43, 95%CI 0.22–0.84) or suffered sICH (OR 0.08, 95%CI 0.01–0.67) were also less likely to experience favorable discharge. There was a trend for favorable discharge among the elderly who received IV tPA (OR 1.76, 95%CI 0.86–3.58), and a trend for unfavorable discharge with age (OR 0.94 per year, 95%CI 0.87–1.01).

In multivariable logistic regression analysis adjusted for age, admission NIHSS, pre-stroke dementia, IV tPA, IAT, and sICH, only NIHSS (OR 1.13, 95%CI 1.06–1.22) and dementia (OR 5.64, 95%CI 1.88–16.89) independently predicted in-hospital mortality (Table 2, model 2). All patients with sICH (n=10) died on admission for their index event; therefore, we were unable to evaluate the independent effect of sICH in multivariable analysis. Limited stratified analysis showed that there was no difference in likelihood for death between non-demented and demented patients with sICH ($p < 0.7$). Furthermore, only NIHSS (OR 0.90 per point, 95%CI 0.85–0.96) and dementia (OR 0.32, 95%CI 0.11–0.95) were independent predictors of unfavorable discharge among the elderly treated with reperfusion therapy (Table 3, model 2).

Discussion

Among the elderly treated with reperfusion therapy for acute stroke at our large, tertiary care center, pre-stroke dementia was a powerful independent predictor of in-hospital mortality and unfavorable discharge. These novel data emphasize the importance of patient selection and consideration of outcomes when establishing the efficacy of acute stroke treatment options. The notion that functional outcomes are poor in most elderly despite treatment[16] could be reevaluated based on the newly discovered role of pre-stroke dementia in this group of patients. Considering that overall stroke severity is greater in the elderly and that it independently affects stroke outcomes[13], they should not be generally denied the chance to benefit from thrombolytic therapy. This idea is further supported by recent results showing a benefit of IV tPA in the very elderly[17]. New factors such as the role of pre-existing dementia could weigh into the individualized risk/benefit analysis for patient selection for reperfusion therapy.

In the general patient population, dementia is known to be associated with longer mean hospital stay, higher intra-hospital, and overall mortality[18]. For primary ICH, dementia is an independent powerful predictor of poor functional outcome, and has been incorporated into a prediction tool[19]. In AIS, disturbance of consciousness in elderly hospitalized patients predicted in-hospital-mortality, however without distinction of whether the disturbance in consciousness existed prior to hospitalization or occurred as a new symptom[20]. Furthermore, pre-stroke institutionalization[21] and pre-existing disability[13] independently predicted three-month disability and poor discharge condition in patients over age 80, respectively; however, no details about the characteristics of the condition leading to disability were provided. Based on our data, prestroke dementia may be the common variable linking pre-existing institutionalization or disability as well as in-hospital disturbance of consciousness with poorer outcomes.

In our study, the likelihood of mortality and unfavorable discharge increased in subjects with more severe strokes (higher admission NIHSS score) and in presence of pre-stroke

dementia. Patients who received IAT or suffered sICH were also less likely to be discharged to a favorable destination; however this lost significance in multivariate analysis.

With or without acute stroke treatment, mortality is higher in elderly patients[21]. In our study, the in-hospital mortality rate among patients ≥ 80 treated with reperfusion therapy was 35%, similar to prior reports[22]. As a novel finding, our data indicate a strong independent association of pre-stroke dementia with in-hospital mortality amongst elderly patients with acute stroke treated with reperfusion therapy, and provide evidence that pre-existing dementia is one of the clinical characteristics which should strongly be considered prior to administering reperfusion therapy.

Due to different outcome measures, our rates of favorable discharges cannot be directly compared with data from other series showing lower rates of favorable outcomes between 20–38% for patients above 80 treated with IV tPA[8, 9]. A discrepancy could in part be explained by selection bias in prior studies where elderly patients were treated according to the physicians' selection. In our cohort, all subjects were selected for IV or IA thrombolysis based on the uniform, institutional protocol which does not exclude subjects from treatment based on age. The large proportion of elderly stroke patients with favorable discharge after reperfusion therapy in our series underscores that outcome in octogenarians and older is not uniformly poor. Furthermore, age was not associated with outcome; therefore, age may predict poor outcome when evaluating all age groups, but not beyond a certain cut-off age, as in our series greater than 80 years.

Current evidence suggests that reperfusion therapy is safe in the elderly population when selected appropriately[23]. Our sICH rate of 6.5% is comparable to the rates of severe hemorrhagic complications, mainly ICH, in younger and older patients in other series[9, 10]. Furthermore, the risk of sICH in our series was not significantly different with respect to treatment modality, as reported previously[24]. Symptomatic ICH occurrence in our study was associated with unfavorable discharge; however, this association was no longer significant after adjustment for age, NIHSS, and treatment modality. In patients with pre-existing dementia, the rate of any hemorrhagic conversion following reperfusion therapy in our cohort was 23%, and only 14.2% of those patients were symptomatic; this is comparable to the sICH rate of 9.7% and rate of 22.6% for any intracranial hemorrhagic complication in a series of elderly patients treated with IV tPA[25,26]. Decreased renal clearance of tPA, frail vasculature, and degenerative vessel wall pathology such as that in amyloid angiopathy have been postulated as possible risk factors for higher risk of ICH in elderly patients who undergo reperfusion therapy[27]; these factors would also explain a higher bleeding risk in brain areas other than the acute stroke territory. Furthermore, complex interactions between the risk factors that contribute both to the risk of vascular cognitive decline and symptomatic cerebrovascular disease (such as ICH) should be considered as major pathophysiological mechanism in this process.[28]

In our study, all patients with sICH died; and although our data do not suggest the link between sICH and death in the elderly with dementia, these conclusions should be interpreted with caution given that the absolute case number of patients with sICH in our series was too small, and the effect of sICH on mortality could not be fully evaluated in multivariate analyses. A larger proportion of elderly stroke patients with dementia is more likely to have underlying vascular pathology such as amyloid angiopathy or vascular cognitive decline, and a possible role of dementia as marker of cerebral vasculopathy prone to sICH after reperfusion therapy requires further investigation.

Main limitations of this analysis are related to its retrospective design, which limits present review of prospectively ascertained data. As a result, we were unable to resolve some of the

questions with regard to a few potential confounders in our data set, such as implied role of blood pressure control on outcomes in this group of patients or pre-stroke medication use.

Relatively small sample size, especially that of the subset of subjects diagnosed with dementia is another drawback of this study that limits interpretation of the study conclusion. Considering that the use of reperfusion therapy in the elderly with AIS, and especially in those with pre-existing dementia is generally low due to lack of the guidelines for this patient subset, we are encouraged that our data from a relatively small, exploratory study would invoke future investigations that would clarify and validate our findings.

Definition of dementia is an additional limitation of this analysis. Even though we aimed to define dementia in the most practical and clinically relevant way for the purpose emergent decision-making during the acute stroke evaluation, we do acknowledge that relying on previously diagnosed dementia or medication use specific for treatment of cognitive impairment is less than ideal. This type of diagnosis is crude, as it does not provide any differentiation between cases of cognitive impairment vs. dementia or subtypes of its underlying pathophysiology. However, misclassification of the dementia cases would have most likely biased our findings toward the null hypothesis and reduced our power to detect the effects of dementia on the outcomes in this cohort, which was not the case in this analysis. Furthermore, testing for dementia during the acute stroke evaluation is neither reliable nor practical, and considering that we suggest using this diagnosis in emergency decision-making, definition of dementia as we proposed it might be acceptable to clinical practice, if validated in the future, prospective studies.

This study did not intend to compare between treatment and non-treatment of elderly stroke patients. Age-matched patients with similar stroke severity who were not treated with thrombolytic agents were unavailable for comparison, as every patient in this database was considered for acute reperfusion therapy based on the presumed clinical benefits of the treatment. In the absence of randomized trials specifically targeting elderly AIS patients, historical observational data from other centers may provide further insight.

Finally, we did not assess long-term functional outcome. Discharge destination in this study provides a surrogate measure of disability and possibly, of rehabilitation potential, as determined by the multi-disciplinary rehab team that evaluated every patient with acute ischemic stroke admitted to our institution. Using their assessment of potential for recovery, we proposed that discharge to an acute rehabilitation facility or home would be considered favorable in at least a proportion of evaluated patients. On the contrary, those subjects who were not deemed to have any rehabilitation potential, and therefore were bound for a skilled nursing facility, hospice, or who died, were obviously considered to have an unfavorable discharge. Whereas a possibility for misclassification between the two groups with regard to their rehabilitation potential may exist, its effect must be negligible at least at the time of discharge. The fact that a sizeable proportion of the patients with dementia were living at a nursing home prior to admission, needs to be considered when using discharge destination as a surrogate marker of outcome. Nonetheless, this limitation does not affect the strong association of pre-existing dementia and mortality, as our primary outcome.

Conclusions

Among the elderly, pre-stroke dementia is a powerful independent predictor of in-hospital mortality and poor outcome. Confirming a benefit of reperfusion therapy in the elderly, who face the greatest risk of ischemic stroke, has remained a challenge, but clarification of clinical factors associated with early death and poor outcome in patients treated with reperfusion therapy can help identify subgroups of patients with increased risks, and those

who are more likely to benefit. This study demonstrates that pre-stroke dementia might indeed be such a clinical factor. If validated in the future large, prospective studies, these data could significantly alter our current approach to baseline stroke assessment and considering likely outcomes after reperfusion therapy in the elderly with acute ischemic stroke.

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Table 1

Patient characteristics and outcomes among 153 acute ischemic stroke patients over 80 years of age treated with thrombolysis.

	All subjects, n (% total)	Diagnosis of dementia		p-value
		No (N=132), n (%)	Yes (n=21), n (%)	
Demographics				
Age (years), mean (SD)	85.8 (4.6)	85.7 (4.7)	86.5 (3.8)	0.49
Sex (male)	47 (30.7)	42 (31.8)	5 (23.8)	0.61
Race (Caucasian)	135 (88.2)	117 (88.6)	18 (85.7)	0.71
Medical History				
Hypertension	115 (75.2)	99 (75)	16 (76.2)	0.9
Hyperlipidemia	51 (33.3)	45 (34.1)	6 (28.6)	0.80
Diabetes mellitus	22 (14.4)	18 (13.6)	4 (19.05)	0.51
Coronary artery disease	47 (30.7)	39 (29.5)	8 (38.1)	0.45
Atrial fibrillation	62 (40.5)	55 (41.7)	7 (33.3)	0.63
Carotid stenosis	6 (3.9)	6 (4.5)	0 (0)	1.0
Prior stroke/TIA	23 (15.0)	20 (15.1)	3 (14.3)	1.0
Stroke characteristics				
NIHSS, median (IQR)	16 (11–20)	15.2 (11–20)	17.8 (11–20)	0.37
Treatment				
IV tPA only	110 (71.9)	97 (73.5)	13 (61.9)	0.3
IA treatment only	54 (35.3)	46 (34.8)	8 (38.1)	0.8
Outcomes				
Mortality	54 (35.3)	41 (31.1)	13 (61.9)	0.012
sICH	10 (6.5)	7 (5.3)	3 (14.3)	0.14
Favorable discharge	83 (54.3)	76 (57.6)	7 (33.3)	0.05
Unfavorable discharge	70 (45.8)	56 (42.4)	14 (66.7)	0.046

Abbreviations: IA – intra-arterial, IQR – interquartile range, IV tPA – interavenous tissue plasminogen activatior, NIHSS – National Institutes of Health stroke scale, SD – standard deviation, sICH – symptomatic intracranial hemorrhage, TIA – transient ischemic attack

Table 2

Predictors of mortality in patients ≥ 80 years who underwent reperfusion therapy for acute ischemic stroke (n=153).

	Model 1**		Model 2**	
	OR	**(95% CI)**	**OR**	**(95% CI)**
Age	1.00	(0.93–1.08)	0.99	(0.91–1.07)
NIHSS	1.14	(1.07–1.21)	1.13	(1.06–1.22)
Dementia	3.61	(1.39–9.37)	5.64	(1.88–16.89)
IV tPA	0.34	(0.17–0.71)	1.39	(0.32–5.99)
IAT	3.43	(1.70–6.92)	3.50	(0.86–14.20)

Model 1* - univariate logistic regression model

Model 2** - multivariate logistic regression model including age, dementia status, NIHSS score, sICH, and treatment with IV tPA or IAT

Abbreviations: IAT – intra-arterial treatment, IV tPA – interavenous tissue plasminogen activatior, NIHSS – National Institutes of Health stroke scale

Table 3

Predictors of favorable discharge in patients ≥ 80 years who underwent reperfusion therapy for acute ischemic stroke (n=153).

	Model 1**		Model 2**	
	OR	**(95% CI)**	**OR**	**(95% CI)**
Age	0.94	(0.87 –1.01)	0.94	(0.87–1.02)
NIHSS	0.90	(0.85–0.95)	0.90	(0.85–0.96)
Dementia	0.37	(0.14–0.97)	0.32	(0.11–0.95)
IV tPA	1.76	(0.86–3.58)	0.38	(0.08–1.85)
IAT	0.43	(0.22–0.84)	0.28	(0.06–1.23)
sICH	0.08	(0.01–0.67)	0.17	(0.02–1.50)

Model 1* - univariate logistic regression model

Model 2** - multivariate logistic regression model including age, dementia status, NIHSS score, sICH, and treatment with IV tPA or IAT

Abbreviations: IAT – intra-arterial treatment, IV tPA – interavenous tissue plasminogen activatior, NIHSS – National Institutes of Health stroke scale, sICH – symptomatic intracerebral hemorrhage