ED Legal Letter™

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TPA in ischemic stroke: Diagnosis is one thing, but timing is everything

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Editor's note: *Public awareness of the symptoms of stroke has increased the frequency of emergency department (ED) visits by patients with this complex chief complaint. Often, subtle symptoms may — or may not — represent a cerebral infarct. This issue of* ED Legal Letter *will review the diagnosis, management, and follow-up of patients with both transient ischemic attack (TIA) and cerebral vascular accidents (CVA). Appropriate diagnosis and treatment will prevent subsequent permanent disability and potential litigation.*

Introduction

Stroke is a devastating disease encountered daily by emergency physicians. Each year, there are more than 750,000 new strokes and 1 million stroke-related hospitalizations in the United States.[1] With 150,000 deaths annually, stroke is the third-leading cause of death in the United States.[2] One-third of patients who suffer a stroke die within a year.[3] Stroke is the No. 1 contributor to long-term disability, as half of survivors are dependent on others for everyday activities.[3] An additional 16% require institutionalized care.[1] The direct and indirect economic impact of acute stroke is no less severe, with costs estimated at $43 million annually.[4] Finally, stroke is an important contributor to depression and neuropsychiatric disorders in the patients it afflicts.[3] Such statistics serve to reinforce the tremendous physical, financial, and emotional toll of this disease.

Emergency physicians stand at the forefront of stroke management, as prompt recognition and appropriate treatment are paramount to optimizing patient outcomes. The attitude toward stroke treatment, which historically has been fatalis-

tic, has changed dramatically in the last decade. In December 1995, the National Institute of Neurological Disorders and Strokes (NINDS) published a study demonstrating improved outcome for stroke patients treated with thrombolysis. Shortly thereafter, tissue plasminogen activator (TPA) was approved by the U.S. Federal Drug Administration as the first drug therapy for acute ischemic stroke. The landscape for stroke management and stroke care thereafter was altered completely. Broad campaigns were organized around the notion of stroke as a "brain attack," analogous to myocardial infarction and requiring prompt lay recognition and response.[5] The public's view was transformed, with heightened awareness of stroke and its potential therapy, a demand for acute treatment, and high expectations for acute care.[6] Subsequently, the emergency physician is faced with the challenge of a strong public desire for a treatment about which controversy brews regarding its efficacy and safety. However, defining the role of TPA in acute ischemic stroke is only one of the challenges facing emergency physicians in stroke management. Others include appropriate identification and management of transient ischemic attack (TIA) and differentiation of stroke mimics from stroke syndromes.

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Management of TIA

Stroke After TIA. *Stalmer v. Hamrick, et al.*[7] Jacquelyn Stalmer, a 52-year-old female, presented to a San Diego urgent care center complaining of headache, right-sided numbness, right facial weakness, and tingling in her right fingers and toes. She first noticed the symptoms at work when she dropped the tray she was carrying in her right hand.

The defendant urgent care physician evaluated Ms. Stalmer, finding her to have a completely normal physical examination. He performed no diagnostic laboratory testing or imaging and consulted the patient's primary care physician (also a defendant in the case) to arrange follow-up. Ms. Stalmer was diagnosed with stress vs. possible TIA and discharged with instructions to take an aspirin daily and call her physician if her symptoms worsened.

Later that evening, Ms. Stalmer had recurrence and worsening of her previous symptoms, and called her primary physician. He instructed her to go back to sleep and that he would see her in the morning. Ms. Stalmer subsequently suffered a stroke, with a resultant permanent hemiplegia.

Attorneys for Ms. Stalmer argued that the defendants were negligent for not hospitalizing her, not performing magnetic resonance imaging (MRI), and for not placing her on heparin. Defense attorneys argued that aspirin was reasonable treatment for a TIA. The jury returned a verdict for the defense; however, plaintiff attorneys motioned for judgment not withstanding, which the trial court granted. A judgment of $2.5 million was ordered on the grounds that experts from both sides agreed that the defendant treatment fell below the standard of care.

Discussion. A TIA is defined as a reversible neurologic deficit attributable to a decrease in cerebral perfusion that resolves within 24 hours. A rapid recovery of normal function is one of the most important characteristics in defining a TIA.[8,9] A large proportion of TIAs last fewer than 10 minutes, with a vast majority resolving within one hour.[8] Only 2% of patients who have deficits that last longer than 90 minutes will have complete spontaneous resolution

of their symptoms.[9] TIAs exist on a continuum with stroke as they arise from the same pathophysiologic process. The vast majority of TIAs are thromboembolic secondary to atherosclerosis or cardiac emboli. Despite the concept of reversible deficit, even TIAs with complete clinical symptom resolution can result in subclinical cerebral infarctions that are evident on MRI in up to 50% of patients.[8,9]

Estimates place the annual incidence of TIA in the United States at 200,000-500,000, though the true incidence likely is higher because many episodes never come to medical attention.[9] Patients who experience one or more TIAs have a tenfold increase in the risk of subsequent stroke.[8] Stroke eventually will occur in one-third of patients with a prior TIA.[2] Given these statistics alone, it is obvious that any patient who presents with a TIA warrants thorough evaluation and aggressive treatment and management.

Recognition of TIA offers an opportunity to initiate treatment that may reduce the risk of subsequent stroke; this, then, becomes the primary objective of the emergency physician. Effective prevention of stroke through appropriate identification, evaluation, and treatment of TIAs could substantially reduce overall stroke incidence and the resultant morbidity and mortality.[10] In a recent review by Borg and Pancioli,[8] the authors defined four essential questions that need to be addressed in any patient who presents with a possible transient ischemic attack. First, does the patient with a transient neurologic deficit truly have a TIA? Second, what is the appropriate testing necessary if a TIA is suspected? Third, when is antithrombotic or antiplatelet therapy appropriate, and for which patients? Finally, can the patient with a TIA safely be discharged from the ED?

Ms. Stalmer's attorneys in the case described above focused on these same four questions, alleging that the diagnosis of TIA was missed, appropriate testing (MRI) was not performed, and appropriate treatment (heparin) and disposition (hospitalization) were not provided. These same themes repeatedly are seen in malpractice cases dealing with TIAs and their management. The emergency physician is, therefore, compelled to address these questions to provide excellent patient care and secondarily reduce malpractice risk.

Retrospectively, as is often the case in emergency medicine, it is obvious that Ms. Stalmer had a TIA, particularly as she went on to complete a stroke. The diagnosis of TIA, however, can prove to be extremely difficult. It is not always clear at the time of initial evaluation that a TIA has occurred. Symptoms often are resolved completely by the time the patient presents to the ED. Symptoms can be vague and nondescript. Physical exam findings and even standard computed tomography (CT) imaging often are normal. Even practitioners evaluating the same patient frequently disagree whether a TIA occurred.[9]

Table 1. Differential for Stroke/TIA/ Stroke Mimics

- Factitious disorders (i.e., conversion disorder)
- Hemiplegic migraines
- Hepatic encephalopathy
- Hyperglycemia
- Hypertensive encephalopathy
- Hypoglycemia
- Intracranial abscess
- Intracranial tumor
- Multiple sclerosis
- Nonconvulsive status epilepticus
- Nonvascular conditions that may resemble an acute stroke syndrome
- Seizure
- Seizure with postictal paralysis (Todd's paralysis)
- Subarachnoid hemorrhage
- Subdural hematoma
- Trauma (closed head injury)
- Vertigo (i.e., benign positional vertigo)

The differential diagnosis of TIA includes a host of diseases. These include, but are not limited to, syncope, seizure, Todd's postictal paralysis, migraine headache, multiple sclerosis, subarachnoid hemorrhage, Bell's palsy, intracranial neoplasm, trauma, various metabolic conditions, and functional disorders. **Table 1** provides a more complete listing of the differential for TIA, stroke, and stroke mimics.

Diagnosing TIA and differentiating it from the large group of disorders that can present with a transient neurologic deficit require an organized and logical approach. First, an attempt should be made to match signs and symptoms with known stroke syndromes (i.e., vertebral-basilar, middle cerebral artery, etc.). Next, a patient's risk factors should be assessed. **Table 2** lists risk factors for TIA and stroke. Finally, careful consideration should be given to all plausible alternative diagnoses. This will help avoid premature closure on a diagnosis prior to thoughtful evaluation of alternatives. Atypical presentations should be treated as TIA, if TIA is the most likely and the most

Table 2. Risk Factors for Stroke/TIA

- Age older than 60 years
- Atherosclerotic vascular disease
- Atrial fibrillation
- Carotid stenosis
- Diabetes mellitus
- Heavy alcohol use
- History of TIA or prior stroke
- Hyperlipidemia
- Hypertension
- Male sex
- Race (African-American > Caucasian)
- Smoking

threatening etiology. Functional disorders (e.g., stress, conversion disorder, etc.), as had been considered in Ms. Stalmer's case, always should be diagnoses of exclusion, with all reasonable medical causes of the patient's symptoms ruled out.

Once diagnosis of TIA is suspected, timely and appropriate work-up must be completed. Unfortunately, testing and evaluation guidelines offer little specific guidance for the emergency physician.[10] Stroke literature supports a two-tiered battery of testing for patients with TIA.[2] First-tier testing should be completed at the time of presentation or shortly thereafter (within 24 hours), and includes laboratory evaluation with a complete blood count, basic chemistry panel, blood glucose, prothrombin and partial thromboplastic time, and a sedimentation rate. Also recommended is an electrocardiogram (ECG), noncontrast head CT, and noninvasive arterial imaging of the carotid arteries using either ultrasound or MRI.

Second-tier testing would include studies such as transthoracic or transesophageal echocardiogram, MRI with or without angiography, ambulatory electrocardiographic monitoring, a cerebrospinal fluid analysis, a hypercoagulable work-up, and cerebral angiogram. These second-tier tests are not all completed routinely for patients with a suspected TIA but are instead selected on a case-by-case basis, depending on the patient's history, risk factors, and prior work-up. While the majority of EDs, even those in smaller community settings, have access to laboratory testing, basic ECG, and head CT, emergent imaging of the carotids often is not available. So, if carotid imaging is not immediately available, what is a reasonable time frame for its completion? Even in consensus guidelines on the management of TIA, recommendations for timeliness of completion of carotid ultrasound are not delineated clearly. The American Heart Association recommends prompt imaging of the carotids by ultrasound, MRI, or CT angiography.[9] The National Stroke Association describes imaging of the carotids as "urgent," but again, no specific time frame is provided for guidance. While no specific recommendations exist, the fact that carotid doppler imaging is a first-tier test suggests it should be completed within 24 hours. Ms. Stalmer's attorney's allegations that she should have had an MRI at the time of her evaluation are unfounded and not supported by current recommendations. The fact that laboratory testing and head CT were not performed, however, could be construed as being below the standard of care for basic evaluation of patients presenting with a suspected TIA.

Stroke With Death After TIA. *Anonymous v. Anonymous*.[11] A 55-year-old college professor was teaching when he experienced visual changes in his left eye, headache, and right leg numbness. His symptoms lasted for several hours, but resolved later that evening. He was concerned about a possible stroke, so he saw his physician the next day, a Friday. A CT scan of the head was scheduled for the following Monday. That evening, he suffered a massive stroke and was not found for two days. He died four days later. Suit was brought, with the case ultimately being settled for $600,000.

Discussion. Although few specific recommendations on the timing of initial work-up for a patient with TIA exist, the tragic case above underscores the importance of expedited evaluation for such patients. The most compelling evidence to this end was a study in 2000 by Johnson, et al., examining the short-term prognosis for patients diagnosed in the ED with TIA.[10] In this study of 1707 ED patients, 10.5% completed a stroke within 90 days, with a striking 5.3% of patients completing a stroke within two days of ED evaluation.[10] When all adverse events (i.e., stroke, congestive heart failure, acute myocardial infarction, unstable angina, ventricular dysrhythmia, recurrent transient ischemic attack, and death) were considered, the combined risk for such adverse affects in patients presenting to the ED with TIA was 25.1% in the first 90 days. The authors concluded that TIAs are ominous predictors of future morbidity and mortality, carrying a substantial short-term risk of stroke, hospitalization for cardiovascular events, and death.[10] Given the data, it is reasonable to regard TIAs as analogous to unstable

angina, and the high risk for catastrophic progression is such that primary evaluation and management ought to be completed at the time of presentation.[8]

Once it has been determined that a patient likely has had a TIA and appropriate first-tier work-up has been initiated, treatment and disposition must be considered. Aspirin is considered standard medical therapy for any patient who has had TIA. Aspirin has been shown in studies to reduce the long-term risk of stroke and cardiovascular events after a TIA or stroke by 22%.[9] Interestingly, however, no study has shown aspirin's effect in the immediate short term after TIA. Despite this, patients without evidence of hemorrhage on CT and without contraindications to aspirin therapy should be started on daily aspirin therapy after a TIA. Dose recommendations range from 80 to 325 mg; however, no consensus on specific dosing exists.[9] Other antiplatelet agents available include clopidogrel, ticlopidine and aspirin/dipyridamole. These agents generally are second-line antiplatelet agents used for patients with contraindications to aspirin therapy or those with recurrent TIA while on aspirin.

With regard to antithrombotic therapy, the attorney for Ms. Stalmer alleged that his patient should have been initiated on heparin therapy. There is little evidence to show that heparin improves any important outcome measures in patients with TIA. Its routine use in all patients with TIA is not recommended.[8] Heparin may be beneficial in patients who have TIAs that are rapidly increasing in both frequency and severity (crescendo TIAs). Heparin also may be of benefit in those patients who are having TIAs while on antiplatelet agents. Finally, heparin therapy is recommended for patients who present with atrial fibrillation of uncertain duration with a TIA.

Determining disposition for patients with TIAs is particularly challenging. Given the extreme morbidity of stroke, some authors advocate that few, if any, patients who present with TIA should be discharged from the ED.[8] Other authors state that interventions such as emergent carotid ultrasound and hospitalization for all patients with TIA are expensive and may not be cost-effective if utilized in all cases of TIA.[10] Unfortunately, no study has identified a reliable risk stratification strategy defining subgroups of low-risk patients who can be managed safely as outpatients. From a practice standard perspective, management of TIA patients is highly variable, both within emergency settings and in the primary care arena. Despite compelling data from Johnson regarding poor short-term prognosis for patients with TIAs diagnosed in the ED, a study by Goldstein showed that, of patients presenting to a primary care practice with TIA symptoms, only 23% were emergently imaged with CT or MRI and only 2% were admitted to the hospital.[12] A study by Henneman and Lewis[13] examined the practice of hospitalization for patients with TIAs. Twenty-seven percent of patients whose admissions were termed "justified" by study criteria did not develop those criteria until after the patients left the ED, suggesting a progression of disease during their hospital stay. The authors concluded that there exists a subset of patients with stroke and TIA who ultimately deteriorate, but that adequate predictors for identifying this group do not exist. Interestingly, 10% of patients in this study admitted with a diagnosis of TIA did not have a TIA or stroke. The authors cited this high occurrence of alternative diagnosis as another motivator for admission.

A highly variable practice standard in conflict with the grave outcome data described in the literature, coupled with notoriously ambiguous guidelines, makes the disposition decision facing emergency physicians for the patient with a TIA a difficult one. However, a rational solution can be suggested. Patients with high-risk criteria for subsequent development of a stroke generally should be managed as inpatients. These criteria were defined by Johnson[10] and include the following: age older than 60 years, a history of diabetes, a deficit involving weakness or speech difficulty, and a deficit lasting more than 10 minutes. While these criteria need prospective validation to be a predictive model, all were independent risk factors for subsequent development of stroke in patients who had presented with a TIA.[10] Secondly, hospitalization should be strongly considered for patients who cannot complete first-tier evaluation within 24 hours, including noninvasive evaluation of the carotid arteries. It is important to identify critical carotid artery stenosis in patients with TIA symptoms as early carotid endarterectomy in those with greater than 70% stenosis has been shown to prevent subsequent stroke and improve outcome.[9]

Finally, patients in whom the diagnosis of TIA is unclear or those with symptoms of crescendo TIA should be managed as inpatients. Hospitalization may hasten testing, specialty evaluation, and initiation of therapy. The benefit of early neurologic consultation is unknown. Careful consideration of the resources of one's own ED and inpatient hospital

setting, access to outpatient testing, and access to outpatient primary care providers and neurology consultants all need to be considered in deciding whether a TIA patient safely can be managed as an outpatient.

Stroke Diagnosis and Stroke Mimics

Stroke Misdiagnosed as Migraine Headache. *Doe v. Roe*.[14] A 53-year-old female presented to the ED of the defendant hospital on Dec. 6, 1998. She complained of right-sided weakness, slurred speech, and headache. She was examined by the defendant physician, who diagnosed her with migraine headache even though she had no prior history of migraines. She was discharged from the ED and collapsed from a stroke the next day. She suffered permanent disability, as she is unable to walk and has hemiparesis of the upper and lower extremities and a prominent cognitive deficit. The patient brought a suit against the defendant physician and hospital, alleging failure to diagnose TIA. The plaintiff's attorneys surmised that had treatment been started on the day of the presentation, both the stroke and its resulting morbidity would have been avoided or substantially decreased. The defendant maintained that the standard of care had not been breached and that there was no causation of damages. The case was settled for $1.215 million.

Stroke Misdiagnosed as Vertigo. *Fernandez v. University of Pennsylvania, et al*.[15] A 57-year-old male with a history of a prior stroke presented to his primary provider complaining of headache, blurred vision, dizziness, weakness, and throbbing in the left eye. He was referred to the ED by his primary provider for admission. His primary physician described him as a "walking time bomb" with multiple medical problems, already on clopidogrel for stroke prophylaxis, and in need of "admission to a neurologist." The patient was seen in the ED, diagnosed with vertigo, given standard treatment, and dismissed. After several return visits to the ED, he subsequently developed slurred speech, incontinence, right facial numbness, and inability to walk without a walker. Ultimately, he was diagnosed with a stroke. Mr. Fernandez brought suit for failure to diagnose stroke and the loss of opportunity to give TPA, alleging this intervention could have significantly improved his outcome. The case went to a jury, which awarded $5 million to Mr. Fernandez.

Discussion. In the era of rapidly developing stroke therapy, it increasingly is important for the emergency physician to quickly and reliably make the diagnosis of stroke. As with TIAs, failure to diagnose a stroke and the subsequent delay in therapy can lead to devastating consequences for the patient, as in the case outlined above. Conversely, administration of thrombolytic therapy to patients with a "stroke mimic" — a nonvascular disease process that appears as a stroke syndrome — could be deadly. Such stroke mimics must be considered in any patient presenting with an acute neurologic deficit.

Studies have shown that emergency physicians and general practitioners accurately can make a diagnosis of stroke in the vast majority of patients.[16] However, estimates place the rate of stroke misdiagnosis at 2-12%.[13] The most common entities misdiagnosed as stroke include seizure, seizure with postictal paralysis, intracranial neoplasm, complicated migraine headache, systemic infection, metabolic disturbance, and psychogenic paralysis.[17,18]

The first step in differentiating stroke from one of the many stroke mimics is a sound understanding of stroke subtypes. Hemorrhagic strokes account for 15-20% of all strokes and include intraparenchymal hemorrhage, aneurysmal rupture, and bleeding from arteriovenous malformation.[19] Ischemic strokes account for 80-85% of strokes, with 60% being thrombotic with a resultant *in situ* inclusion of an atherosclerotic vessel. Forty percent are embolic with a proximal, most often cardiac, source. Fewer than 5% of strokes are caused by a collection of disorders listed in **Table 3**. Among the more common of these infrequent causes of stroke are: complicated migraines, arterial dissection, cocaine, sickle cell disease with vasocclusion, and antiphospholipid syndrome. **Table 1** highlights the common stroke mimics, including metabolic disorders, central and peripheral nervous system disorders, and psychiatric entities. Detailed below are several of the more common stroke mimics.

Migraine Headache. The vasospasm associated with migraine headache can precipitate a true stroke syndrome. However, there exists an entity known as hemiplegic migraine in which paresis outlasts the headache, yet no true stroke occurs. This syndrome is nearly impossible to distinguish from true stroke on a first-time presentation, as a history of stereotypic attacks is necessary to confirm the diagnosis of hemiplegic migraine.

In *Doe v. Roe,* the plaintiff was a 53-year-old female with acute neurologic symptoms and no prior history

of migraine headache. New onset of migraine headaches in the sixth decade would be rare. Diagnosis of migraine headache in such a patient would be a diagnosis of exclusion after other important intracranial or metabolic entities were excluded. The consequences of settling on a diagnosis of a common, yet benign process were significant, given the more threatening diagnosis of stroke that was overlooked.

Hypoglycemia. Transient hypoglycemia may cause hemiplegia and aphasia without altered mental status. This syndrome may be seen in alcoholics with hypoglycemia rather than the more common presentations of confusion, decreased level of consciousness, and coma.[17] A bedside glucose should be checked routinely in any patient presenting with altered mental status or a focal neurologic deficit.

Intracranial Mass Lesions. Chronic subdural hematoma, intracranial abscesses, and primary or metastatic brain neoplasms can present with acute onset symptoms. In one review of patients presenting to the ED who were subsequently newly diagnosed with a brain tumor, 6% had symptoms of fewer than one day's duration.[17]

Seizures. Seizure is one of the most common entities mistaken for stroke. Postictal paralysis (Todd's paralysis) usually is brief, but can last up to 48 hours. To further confuse matters, seizures may present as a complication of an acute stroke or develop in a patient with a history of strokes. Generally, seizures are identified after a more complete history, additional testing (i.e., electroencephalogram [EEG]), or subsequent development of more seizures.

Toxic Metabolic Encephalopathy. Hyponatremia, hepatic encephalopathy, and hyperglycemia all can present with focal neurologic deficits. Hyperglycemia specifically has been associated with aphasia, homonomous hemianopsia, hemisensory deficit, and hyperreflexia, including positive Babinski's reflex.

Functional Disorders. Conversion disorder is the most common feigned or factitious entity that can present as a stroke-like syndrome. As with other psychiatric disorders, this should be a diagnosis of exclusion. Of patients seen in the ED with conversion disorder, 30% present with paresis, paralysis, or a movement disorder.[17]

Vertigo. Patients with benign positional vertigo or other vertigo syndromes can be mistakenly diagnosed as having a stroke syndrome. Posterior circulation TIAs and strokes will present with vertigo, ataxia, and, sometimes, syncope. Distinguishing benign causes of vertigo from the more threatening vertebrobasilar insufficiency is crucial in avoiding significant patient morbidity and mortality.

Table 3. Infrequent Causes of Stroke

- Amphetamines
- Arterial dissection
- Arteritis (giant cell)
- Antiphospholipid disease
- Bone marrow transplant
- Coagulopathies
  - — Thrombotic thrombocytopenic purpura (TTP)
  - — Idiopathic thrombocytopenic purpura (ITP)
  - — Protein C disease
  - — Protein S disease
  - — Antithrombin III disease
- Cocaine
- Migraine headache
- Postpartum stroke (eclampsia)
- Sickle cell disease

In *Fernandez,* Mr. Fernandez's history of prior stroke was a significant risk factor for subsequent stroke. Mr. Fernandez also had multiple ED visits for the same complaint. The natural tendency is to assume the initial diagnosis is accurate in a patient who returns to the ED. The emergency physician should guard against this tendency and view a return visit as an opportunity to make a new diagnosis rather than repeating an errant one.

Patients who present with symptoms of stroke with an altered sensorium more commonly have a stroke mimic.[17] While further differentiation is largely based on history, ancillary testing with labs and imaging has been shown to improve sensitivity and specificity in stroke diagnosis. A study by Liebman looking at 400 consecutive patients presenting to the ED who initially were diagnosed with stroke based on history and physical alone found that 19% actually had stroke mimic.[20] A subsequent study by Kothari added lab testing and CT imaging to history and physical, and the incidence of stroke mimics was noted to be 4%.[21] A final study by Ay utilized history and physical, labs, CT, and MRI, and the misdiagnosis of stroke was reduced to 1-2%.[22] Each intervention, including lab evaluation, CT, and MRI, increases the specificity of the diagnosis of ischemic stroke.

Thrombolytics in Stroke

TPA. The NINDS trial found that TPA could safely

Table 4. Indications, Contraindications, and Dosing for TPA in Acute Ischemic Stroke

INCLUSION CRITERIA

- Onset of ischemic stroke with clearly defined onset
- Neurologic deficit measurable on the National Institute of Health Stroke Scale
- CT scan without evidence of intracranial hemorrhage

EXCLUSION CRITERIA

- Absence of stroke or head trauma within preceding three months
- Major surgery within 14 days
- History of intracranial hemorrhage
- Systolic blood pressure greater than 185 mmHg or diastolic blood pressure greater than 110 mmHg
- Rapidly improving or minor symptoms
- Symptoms suggestive of subarachnoid hemorrhage
- Gastrointestinal or urinary tract hemorrhage within 21 days
- Arterial puncture at a noncompressible site within seven days
- Seizure at onset of stroke
- Use of anticoagulants or heparin within 48 hours of onset
- Elevated PTT or PT greater than 15 seconds
- Platelet count below 100,000
- Glucose less than 50 mg/dL or greater than 400 mg/dL

TPA REGIMEN

- 0.9 mg/kg (maximum 90 mg)
- 10% of dose as bolus with remaining 90% as constant infusion over 60 minutes

be administered to patients with acute ischemic stroke and resulted in an 11% increase in the number of patients who recovered with minimal to no functional sequelae.[23] TPA was approved by the U.S. Food and Drug Administration six months after NINDS data publication and was incorporated into American Heart Association guidelines for the treatment of acute ischemic stroke in 2000.[24] Based on these recommendations, TPA use has been considered by many to represent the standard of care for the treatment of patients who qualify for its administration. This recommendation, however, has been controversial, with many practitioners questioning the evidence behind the recommendations.[25,26] The controversy centers on the conflicting conclusions reached by the major trials studying the efficacy of thrombolysis. All of the trials evaluating streptokinase (ASK, MAST-E, MASTI-I) found an unfavorable risk:benefit ratio.[27-29] Of the trials evaluating TPA, only the NINDS study found a clinical benefit with treatment.[23] The European Cooperative Acute Stroke Study (ECASS) revealed an adverse safety profile precluding TPA use.[30] Two other trials demonstrated no clinical benefit with TPA.[31,32] Baseline differences between the two treatment arms in the NINDS trial have raised questions about the positive findings of this single trial. Furthermore, subsequent studies evaluating community-based use in Cleveland and Connecticut have found safety profiles that were dramatically worse than that seen in clinical trials.[33,34] The Canadian Association of Emergency Physicians, American Academy of Emergency Medicine, and American College of Emergency Physicians have questioned the recommendations implying that failure to administer TPA represents a deviation from standard of care.[35-37] Despite this, many emergency physicians feel they are compelled to administer TPA to patients who qualify for its use. Furthermore, media coverage about its efficacy has raised patient and family member expectations regarding the use of TPA. The decision to administer TPA for treatment of acute ischemic stroke is thus a difficult one for the emergency physician.

Failure to Recommend TPA Therapy-Hemispheric Stroke. *Paige v. HCA Health.*[38] Mr. Paige suffered an ischemic stroke in February 1998 and was transported to Blake Medical Center, where he was evaluated by Dr. Robert Gessner, an emergency physician. After examining Mr. Paige, Dr. Gessner consulted the on-call neurologist, Dr. Steven Norris, and contacted Mr. Paige's son and daughter-in-law, both of whom were physicians at the hospital. Dr. Norris testified that prior to admitting Mr. Paige to the ICU, he discussed treatment alternatives with the patient and his son, and they decided on treatment with heparin. Overnight, Mr. Paige's family requested consultation with a neurologist with whom they were familiar. It later was determined that Mr. Paige had been a candidate for TPA therapy, though Dr. Norris later testified that Mr. Paige was not a candidate because his symptoms were improving. Mr. Paige never fully recovered from his stroke. Mr. Paige and his wife filed suit against Blake Medical Center and Drs. Gessner and Norris for failure to recommend thrombolytic therapy. A settlement for $50,000 was reached with Blake Medical Center. Claims against Dr. Gessner were dismissed prior to trial. A defense verdict was returned for Dr. Norris.

Discussion. Administering TPA to patients with acute ischemic stroke remains controversial. Among practitioners, there are both strong opponents and proponents of TPA use. Regardless of one's personal view regarding the true efficacy of TPA, it is essential that

treatment with TPA, as well as alternative therapies, be discussed with any patient who is a potential TPA candidate (i.e., presents within three hours of symptom onset). Family members should be included when available, and the nature of these discussions should be documented clearly in the ED record. This not only is true if the patient meets all requirements for TPA therapy, but also is applicable when the patient has a contraindication, since some contraindications may be viewed as subjective. Dr. Norris' testimony that he had enlisted the patient and his physician/son in the decision-making process regarding therapy certainly strengthened his case. It is critical that such discussions be documented in the medical record.

As is true for any therapeutic intervention, it is imperative that emergency physicians be familiar with the indications and contraindications for TPA use in the setting of acute stroke. **Table 4** provides inclusion and exclusion criteria as well as dosing information for the use of TPA in ischemic stroke, as delineated in the NINDS trial.[23] To be considered for treatment, TPA must be administered within three hours of symptom onset. The NINDS trial demonstrated favorable outcome and risk-benefit ratio only for patients treated within a three-hour window of symptom onset.[23] Given this narrow three-hour window, determining the exact timing of symptom onset becomes paramount in establishing eligibility for treatment. TPA administered outside of the three-hour therapeutic window is associated with a high rate of adverse outcomes.[30-32] Underestimation of the time of onset can lead to increased bleeding risk[32] and increased morbidity and mortality, negating any of the benefits demonstrated in the NINDS trial. Other contraindications to TPA therapy include spontaneous symptom improvement; signs of hemorrhage on head CT; poorly controlled blood pressure, with systolic and diastolic blood pressures greater than 185 mmHg and 110 mmHg, respectively; concurrent anticoagulant therapy; and thrombocytopenia.

Cerebellar strokes can present with subtle symptoms, making their diagnosis difficult. None of the major studies evaluating TPA for stroke specifically evaluated their efficacy for this stroke subtype. Given the static bleeding risk associated with TPA administration and the minimal tolerance for edema or mass effect in the posterior fossa, it could be hypothesized that outcomes would be worse for this stroke subtype were hemorrhage to occur post-TPA administration. Furthermore, because presentations often are more subtle, determining the exact time of symptom onset often is difficult.

For every case in which TPA is considered, the emergency physician must take into account the risk-benefit ratio for the patient. If the patient's symptoms are mild and improving, the potential benefits of TPA drop considerably while the real risks remain constant. Patients who receive TPA despite having a contraindication have a significantly increased incidence of suffering an adverse outcome.[34]

Hemorrhagic Stroke after TPA. *Harris v. Oak Valley Hospital, et al*.[39] Wilma Harris was a 65-year-old female who presented to Oak Valley Hospital's ED with stroke-like symptoms and elevated blood pressure. A CT scan was promptly performed and revealed an ischemic stroke for which she was administered TPA. She developed an intracerebral hemorrhage, resulting in residual neurologic deficits, including difficulty with ambulation and speech. The plaintiff claimed the residual neurologic deficits were caused by the hemorrhage, which she alleged was caused by inappropriate administration of TPA. She contended that her blood pressure was not adequately controlled and that her symptoms were rapidly resolving even prior to being given the drug. The defense argued that the patient and her family had been given appropriate informed consent and that her blood pressure adequately was monitored and in the appropriate range until she developed the hemorrhagic stroke. The defense expert argued that studies have failed to demonstrate significant correlation between elevated blood pressure and hemorrhage due to TPA, leading to a question of causation. The jury returned a decision for the defense.

Discussion. One of the most influential barriers to the widespread use of TPA for acute ischemic stroke is the narrow risk-benefit ratio associated with its use. The most common serious complication with its use is hemorrhage, with intracranial hemorrhage causing the most adverse outcomes. The NINDS trial demonstrated that there was a 12% absolute increase in the number of patients with minimal to no disability at three months for those given TPA as compared to placebo. This was balanced by an 11% increase in all intracranial hemorrhages and a 6% absolute increase in the number of patients with symptomatic intracranial hemorrhage, of which nearly 50% were fatal. Mortality rates, however, in both the treatment and placebo groups were comparable.[23] In the second ECASS study, there was a 2.5-fold increase in symptomatic intracranial hemorrhage in the treatment

group, but again, no increase in mortality.[31]

With widespread community use, the risks of adverse outcomes may be even greater than those seen in the tightly controlled environment of a clinical trial. A registry of all patients in the Cleveland area who received TPA found the incidence of both symptomatic and asymptomatic intracranial hemorrhage to be more than twice that seen in the NINDS trial.[33] Likewise, a registry of patients treated with TPA in Connecticut found a threefold increase in the incidence of serious hemorrhage and a twofold increase in the mortality rate compared to the NINDS trial.[34] Of note, two-thirds of the patients treated with TPA in this trial had major deviations from the protocol outlined in the NINDS trial. Outcomes of those who had major protocol violations were substantially worse than those without protocol violations. This underscores the importance of ensuring that patients for whom TPA is considered meet criteria for administration. Failure to exclude patients based on contraindications is likely to substantially increase their risk for adverse outcomes.

With regards to blood pressure and intracranial hemorrhage, a direct causative relationship has not been established between hypertension and adverse outcomes, as was argued by defendant attorneys in this case. However, patients in the Connecticut study who did not meet the blood pressure criteria for TPA had more than a twofold incidence of serious intracranial hemorrhage and death compared to patients without major protocol violations.[34]

Also germane to this discussion are initial CT findings. Ms. Harris' CT was said to have revealed findings consistent with acute ischemic stroke. Many initial findings of early ischemic stroke, such as loss of the insular ribbon, loss of the gray-white interface, and loss of sulci, do not exclude the use of thrombolytic therapy. However, large areas of hypodensity or early signs of cerebral edema and mass effect are more likely to represent irreversible neuronal injury that carries a greater chance of hemorrhagic complication with the use of TPA.[1]

A final issue raised by this case is how to effectively obtain informed consent from TPA-eligible patients suffering an acute stroke. Unlike therapies that offer clear benefit with minimal risk, the inherent bleeding risks associated with TPA necessitate that patients be aware of these risks before being subjected to them.[5] Given the short therapeutic window of three hours, it may be difficult for emergency physicians to adequately explain the details of these risks in a manner that is understandable. This is particularly difficult when one considers that stroke experts cannot agree on how to quantitate the risk-benefit ratio of TPA therapy. This issue can be compounded when the patient is rendered acutely incompetent by the stroke itself and surrogates are relied upon to make a decision of such immense magnitude for their loved one. While authors have opined on the ethics and approach to consent for TPA in acute ischemic stroke,[5] the reality is there is not a simple, well-defined solution to the issue of consent. A keen understanding of risk-benefit considerations based not only on NINDS data, but also on that of other studies in which TPA therapy was employed, will significantly aid the emergency physician in assisting patients in making a therapeutic decision while appropriately obtaining informed consent.

Conclusion

Stroke is a devastating, prevalent disease. Emergency physicians play a key role in acute stroke care. Many challenges are faced by the emergency physician, including proper identification and management of TIAs, differentiation of stroke syndromes and stroke mimics, and navigation of the controversies surrounding thrombolytic therapy. This issue has attempted to provide practical guidance for quality, evidence-based care of stroke patients coupled with sound risk management strategies. As is true in all cases, the greatest protection from medical liability is establishment of physician-patient rapport. Regardless of the treatment strategy chosen, it is essential that the physician explain the presumed diagnosis, rationale for the chosen treatment plan, and signs or symptoms for which to return. Reference to these discussions should be carefully documented. By spending time ensuring that the patient leaves educated, emergency physicians not only can optimize outcomes, but also minimize their risk.

Endnotes

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In Future Issues: **Documentation Errors**

CE/CME Questions

13. Which of the following statements regarding TIAs is *false?*
A. Rapid recovery of function is characteristic of TIAs.
B. TIAs exist on a continuum with stroke.
C. Patients with deficits lasting longer than 90 minutes have a high probability of spontaneous symptom resolution.
D. One study demonstrated that 5% of patients had a completed stroke within two days of a TIA.

14. Which of the following tests is not considered a "first-tier" test in the evaluation of TIA?
A. Glucose
B. Head CT
C. Transesophageal echocardiogram (TEE)
D. Carotid ultrasound

15. Which of the following is true regarding stroke identification and mimic?
A. CT and lab add to the sensitivity and specificity of stroke identification.
B. Seizures in hypoglycemia are rarely encountered in stroke mimics.
C. Migraine headaches cannot result in a true stroke syndrome.
D. Patients with conversion disorder rarely present with focal neurologic findings.

16. Which of the following is/are effective risk management strategies?
A. Admitting all TIA patients unless an expedited outpatient evaluation and follow-up are accessible.
B. Clearly documenting time and content of discussions with consultants regarding recommendations and transfers of care.
C. Providing patients and family members a fair assessment of risks, benefits, and alternatives to TPA administration for acute stroke.
D. All of the above

Answers: 13. C; 14. C; 15. A; 16. D.

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