CASE RECORDS of the MASSACHUSETTS GENERAL HOSPITAL

Case 16-2006: A 72-Year-Old Woman Admitted to the Emergency Department because of a Sudden Change in Mental Status

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PRESENTATION OF CASE

Dr. Emily Senecal (Emergency Medicine): A 72-year-old left-handed woman was transported by helicopter from her home to the emergency department of this hospital because of a sudden change in mental status and left hemiparesis.

On the day of admission, she was well when last seen by her husband at 11:30 a.m. At 12:15 p.m., her son called her at home, and she produced only slurred and unintelligible speech. He called his sister, who notified emergency medical services (EMS). At 12:45 p.m., the daughter arrived at the patient's home, followed shortly by EMS, and they found the patient lying on the floor. She was awake but not moving her left side, and her gaze was deviated to the right. The pupils were round; the right was 5 mm in diameter and reactive to light (constricting to 4 mm), and the left was 3 mm in diameter and reactive to light (constricting to 2 mm). Her speech was slurred, but she provided appropriate "yes" and "no" oral responses. The glucose level on a finger-stick capillary sample was normal. A cervical collar was applied, since the patient had fallen, and two peripheral intravenous lines were placed.

At 12:56 p.m., the EMS providers radioed for air medical response to transfer the patient from her home to this hospital. A helicopter was dispatched at 12:57 p.m.; the air medical operations center simultaneously notified the emergency department of the impending arrival of a patient with presumed stroke. While awaiting arrival of the air medical crew, the EMS providers noticed that the patient's speech and weakness had worsened; because of concern about her ability to protect her airway, they attempted nasotracheal intubation, using as premedication 75 mg of intravenous lidocaine, 2 mg of intravenous midazolam, and 5 mg of intravenous diazepam. This was unsuccessful, and the patient was given oxygen through a nonrebreathing mask.

The air medical crew (a nurse and a paramedic) arrived at 1:20 p.m. They found that the patient's left arm and leg were paralyzed and her speech was slurred. She

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opened her eyes when trying to talk, made incomprehensible sounds, and followed commands regarding her right arm and leg; the score on the Glasgow coma scale was 11 (a score of 3 indicates a deep coma, and 15 that a patient is fully alert and following motor commands), and the National Institutes of Health Stroke Score (NIHSS) was estimated to be 30 (a score of 0 indicates normal function, 20 a major stroke syndrome, and 42 deep coma). The blood pressure was 140/80 mm Hg, the pulse 92 beats per minute, the respirations 14 per minute, and the oxygen saturation 100 percent while the patient was wearing a nonrebreathing mask.

Orotracheal intubation was performed at 1:31 p.m. with the use of topical anesthesia containing 14 percent benzocaine, 2 percent butamben, 2 percent tetracaine hydrochloride, and 0.5 percent benzalkonium chloride (Cetacaine, Cetylite) and supplemented with 50 μg of fentanyl (just under 1 μg per kilogram of estimated weight) intravenously. Despite a repeated dose of 50 μg of fentanyl, the patient reached for the endotracheal tube with her right arm. To prevent extubation during transport, she was given 5 mg of pancuronium (just under 0.1 mg per kilogram of estimated weight) intravenously. The remainder of the transport was without incident. The air medical crew radioed the emergency department with the patient's information and estimated time of arrival.

At 1:45 p.m., the patient arrived in the emergency department and was met by a team of emergency physicians and stroke neurologists. She remained intubated and pharmacologically paralyzed. The blood pressure was 164/76 mm Hg, the temperature 36.2°C, the heart rate 95 beats per minute, and oxygen saturation 100 percent while she was receiving assisted ventilation with a fraction of inspired oxygen of 1.0. Physical examination revealed no evidence of trauma. The pupils were 2 mm in diameter, round, and reacted to light with constriction to 1.8 mm. The change in pupillary reactivity was attributed to the recently administered paralytic agents. A cervical collar was in place. The general physical examination was normal. Since the patient was pharmacologically paralyzed, neurologic examination was not informative.

The patient's family arrived at the emergency department soon after the patient and provided additional history. Two weeks before admission and again two days before admission, the patient had reported 30 minutes of numbness of the left lower portion of her face. The night before admission, she had had a syncopal episode in the bathroom and had fallen and hit her head; she was aware of the event and informed her husband of it the next morning. She had a history of hypercholesterolemia and seasonal allergies. Her only medication was loratadine, and she had no known drug allergies. She had stopped smoking 40 years earlier. Her aunt and a first cousin had had strokes.

An electrocardiogram revealed sinus rhythm. A radiograph of the chest revealed that the endotracheal tube was well placed and the lungs were normal. The results of laboratory tests are shown in Table 1.

At 2:51 p.m., computed tomography (CT) of the head without intravenous contrast medium and CT angiography were performed. The images without contrast medium showed a hyperdense linear focus in the distribution of the main trunk (M1) of the right middle cerebral artery, which corresponded to a focal filling defect on the angiographic images. The findings were consistent with the presence of a clot in the main trunk of the right middle cerebral artery, extending into the first segments (M2 branches).

A management decision was made.

MANAGEMENT

Dr. Stephen H. Thomas: The key features of this case — focal neurologic deficits in the absence of apparent trauma — suggested an acute stroke. Just as time is crucial in cases of injury or myocardial infarction, expedited transport is vital to the optimization of outcomes among patients with stroke. Accordingly, EMS systems have worked to streamline both primary (from the scene) and secondary (from referring to receiving hospitals) transports of patients with stroke.

PRIMARY TRANSPORT OF PATIENTS WITH ACUTE STROKE

Primary transport has been accelerated by emphasizing the urgency of dispatch for patients with suspected stroke.[1] EMS dispatchers are being trained to use stroke-assessment tools validated in the EMS and emergency department settings (e.g., the Cincinnati Prehospital Stroke Scale).[2,3] Secondary transport is becoming more efficient; the air medical service providing transport in this case has reported substantial improvements in the urgency with which referring hospitals arrange interfacility transfer of patients with stroke.[4]

Does the goal of expedited transport to a stroke center justify bypassing closer hospitals? The patient's home, 15 miles from this hospital, was a 10-minute drive from a community hospital that lacked the capacity to perform rapid CT of the head. In the majority of cases of suspected stroke, the primary transport should be on the ground. However, for any time-critical diagnosis, situational logistics (e.g., traffic and the distance to a hospital) may occasionally dictate the need for air transport, and the use of helicopters by EMS has been an important means for extending the reach of stroke care centers.[4-8] In this case, the responding ground EMS personnel had received stroke training, including stroke diagnosis and field triage, from the department of neurology at this hospital and from Boston MedFlight (BMF). Considering the likelihood of the need for tertiary care and since the patient's condition was stable, the paramedics' decision in favor of direct transport to this hospital was wise, since an intermediate stop at the local facility would have added at least a half hour to the interval before arrival at a stroke center.[4]

While BMF was en route to the scene, the deterioration in the patient's condition prompted ground EMS personnel to attempt endotracheal intubation using benzodiazepine sedation. The role of prehospital endotracheal intubation, in general and in this case, is debatable. According to one objective measure, the Glasgow Coma Score of 11, her condition had not deteriorated to the level (indicated by a score of 9 or less) that required endotracheal intubation.[9] However, other findings (e.g., evidence of deteriorating neurologic status) can suggest impending airway impairment and thus dictate the need for intubation. If intubation is likely to be needed, should it be done on the ground or in flight? Successful in-flight airway management was reported in 96 percent of the cases in one study,[9] suggesting that intubation can safely be deferred. In this case, we do not have enough information to determine whether the decision in favor of preflight endotracheal intubation was justified. Two benzodiazepines were administered; lidocaine was also given, presumably because of its neuroprotective effect, though this practice remains controversial.[10] Since the reported success rates of endotracheal intubation by ground EMS personnel using just benzodiazepine sedation is only 63 percent, the failure of the initial attempt is not unexpected.[11]

The use of neuromuscular blockade to facilitate intubation in the field is perhaps the most controversial subject in prehospital medicine. A controlled clinical trial demonstrated that the

Table 1. Laboratory Values on Admission.*

Variable	Value	Normal Range
Sodium (mmol/liter)	140	136–145
Blood urea nitrogen (mg/dl)	21	10–20
Creatinine (mg/dl)	0.9	<1.5
Glucose (mg/dl)	116	75–115
White cells ($\times10^{-3}$/mm^3)	8.0	4.5–11.0
Hematocrit (%)	34.9	41.0–53.0
Platelets ($\times10^{-3}$/mm^3)	287	150–350
Prothrombin time (sec)	11.9	11.1–13.1
Activated partial-thromboplastin time (sec)	24.9	22.1–34.0
Calcium (mg/dl)	9.2	9.0–10.5
Magnesium (mg/dl)	1.9	1.8–3.0
Creatine kinase (U/liter)	97	60–400
Creatine kinase isoenzyme (ng/ml)	Too low to calculate	0.0–6.9
Troponin T	<0.01	0.00–0.09
Albumin (g/dl)	3.6	3.5–5.5
Total cholesterol (mg/dl)	289	<200
Triglycerides (mg/dl)	184	<160
High-density lipoprotein choles-terol (mg/dl)	70	0.80–1.80
Low-density lipoprotein cholesterol (mg/dl)	182	<100
Protein S, functional (%)	89	
Protein C, functional (%)	142	
Anticardiolipin IgG phospholipid	0.2	
Anticardiolipin IgM phospholipid	1.8	
Lupus anticoagulant	Negative	
Activated protein C resistance screen	3.2	

* To convert the values for blood urea nitrogen to millimoles per liter, multiply by 0.357. To convert the values for creatinine to micromoles per liter, multiply by 88.4. To convert the values for glucose to millimoles per liter, multiply by 0.05551. To convert the values for calcium to millimoles per liter, multiply by 0.250. To convert the values for magnesium to millimoles per liter, multiply by 0.4114. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. To convert the values for triglycerides to millimoles per liter, multiply by 0.01129.

use of paralytic agents by EMS teams with limited training yielded successful intubation in only 41 percent of patients.[12] The air medical crew in this case had had extensive airway-management training that supplements traditional lectures and mannequin sessions with experience with both animals and humans (operating room).[13] Implementation of such training is not easy, but programs that include such efforts have reported rates of successful intubation of 97 percent.[9,14] The air medical crew was able to intubate the patient without paralytic agents, underscoring the fact that successful prehospital airway management depends as much on education and experience as it does on access to any particular class of medication. Notably, current and preferred practice both in the emergency department and during air transport would be to perform an intubation facilitated by the use of neuromuscular blockade, with more adjunctive sedation than was used in this case.

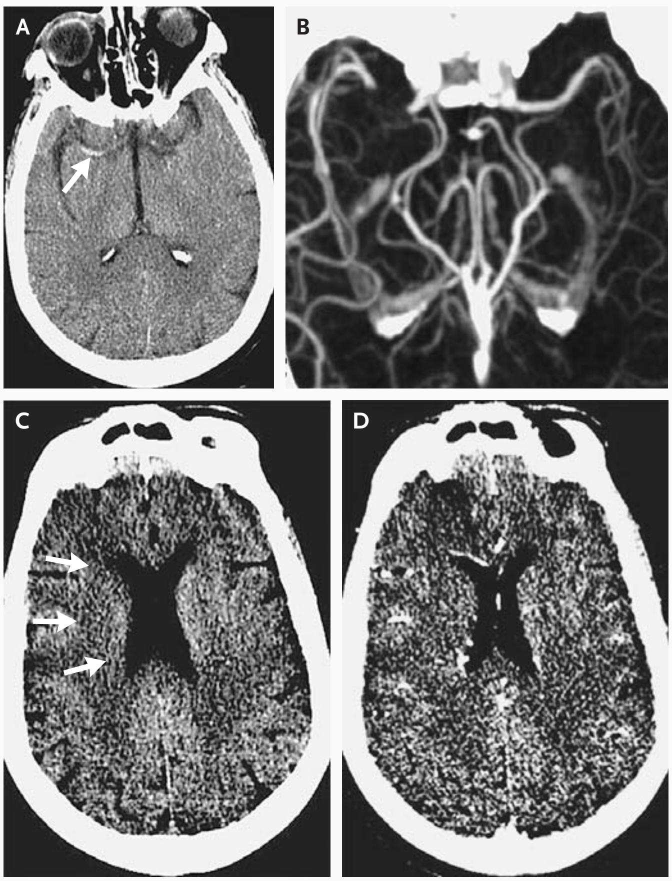

Figure 1. Imaging Studies on Admission.

Unenhanced CT of the brain shows a hyperdense right middle cerebral artery (Panel A, arrow). A concurrent CT angiogram shows a corresponding intraluminal filling defect of the right middle cerebral artery, confirming the presence of a thrombus (Panel B). Unenhanced CT, viewed with narrow window width and center-level display settings, shows subtle loss of differentiation between gray and white matter and acute hypodensity of the right lenticular nuclei, including the caudate head, globus pallidus, and putamen (Panel C, arrows). A corresponding slice from the source-image CT angiogram obtained at admission (Panel D), at the same level as shown in Panel C, shows reduced blood pool and relative hypodensity in this region, suggesting an area of irreversible ischemic injury (infarct core).

USE OF NEUROMUSCULAR BLOCKADE

A paralytic agent was used in flight in this case because of concern that the patient was moving uncontrollably, as evidenced by an attempt at self-extubation. The patient had received two doses each of two sedatives, fentanyl and benzodiazepines, and her vital signs remained stable. Did she require chemical paralysis or simply more sedation? Additional sedation might have obviated the need for long-acting paralytic agents, but sedation takes time, and the risks of inadvertent extubation and other uncontrolled movements by a patient are not to be taken lightly in a helicopter. Nonetheless, the variables for prehospital decision making regarding the need for sedation in paralyzed patients parallel those used in the hospital environment, and prehospital providers must observe the clinical imperative to sedate paralyzed patients adequately. When there is doubt about the adequacy of sedation in a paralyzed patient, additional sedatives should be provided. There is insufficient information in this case to adjudicate with certainty the appropriateness of the use of paralytic agents as mentioned in the case record, but it is a cause for reflection and, potentially, concern.

Dr. Michael H. Lev: A CT of the head performed without the use of contrast medium after the patient's arrival in the emergency department (Fig. 1A) revealed a hyperdense right middle cerebral artery, a highly specific (>90 percent) indicator of acute vascular thrombosis.[15] The dense vessel typically contains a "red" thrombus, a loose network of predominantly red cells with some fibrin, rather than a "white" thrombus, which consists of cellular debris, fibrin, and platelets, but only a few red cells.[16] The presence of a radiologically dense thrombus may help to predict the likelihood of recanalization, since the loosely organized red clot permits better penetration of thrombolytic agents, whereas the more compact, fibrin-rich white clot may hinder thrombolysis because it is less permeable.[16]

The presence of a thrombus in the proximal right middle cerebral artery was confirmed by CT angiography, a routine test at this hospital for all patients with acute stroke (Fig. 1B). The accuracy of CT angiography of the circle of Willis for detecting and delineating proximal intravascular thrombus approaches that of conventional catheter arteriography.[17] Our acute-stroke protocol calls for CT of the head without the use of contrast medium to rule out hemorrhage and identify parenchymal hypodensity, followed by complete neurovascular CT angiography, which includes screening evaluation from the great-vessel origins at the aortic arch through the neck, skull base, and circle of Willis, to the cranial vertex.

Because the images acquired during CT angiography are weighted according to the cerebral blood volume,[18] they can make the subtle, early ischemic lenticular hypodensities present on the unenhanced scan more conspicuous (Fig. 1C, arrows, and Fig. 1D), and like magnetic resonance diffusion-weighted imaging, may identify hypoperfused ischemic brain parenchyma likely to be irreversibly infarcted despite the use of vascular recanalization ("infarct core").[19-22] The sensitivity of CT angiography source images for the detection of large infarct cores approaches that of diffusion-weighted imaging.[19] The sensitivity for the detection of an infarct core on unenhanced CT can be improved by reviewing images with the use of optimized image-display settings.[23]

Dr. Lee H. Schwamm: This 72-year-old left-handed woman had occlusion of the right middle cerebral artery, accompanied by complete dysfunction of the right hemisphere with a gaze preference, left-sided weakness, anosagnosia (lack of awareness of her deficits), and speech that was slurred and at times incomprehensible. She had evidence of a clinical penumbra: a mismatch between the brain at risk (the large amount of electrically dysfunctional but still potentially salvageable brain tissue responsible for her deficits) and the brain destined to die (the small core of brain tissue shown to be irreversibly damaged on CT). She also had evidence of an imaging penumbra: a mismatch between brain regions with perturbed blood flow (delayed or reduced flow) and brain destined to die (Fig. 2). Recent clinical trials have suggested that patients with this type of imaging penumbra may have longer therapeutic windows for intravenous thrombolysis than the three-hour limit used for intravenous tissue plasminogen activator (t-PA).[24]

REASONS TO CONSIDER THROMBOLYSIS IN ACUTE ISCHEMIC STROKE

A randomized clinical trial in the 1990s[25] demonstrated that as compared with patients given placebo, patients treated with intravenous t-PA were at least 30 percent more likely to have minimal or no disability at one year.[26-28] Although intravenous t-PA is associated with an increased risk of symptomatic intracerebral hemorrhage, the risk of death is not increased. A subsequent analysis confirmed the importance of treatment soon after the onset of stroke.[29] On the basis of these data, administration of intravenous t-PA is now recommended within 180 minutes after an acute ischemic stroke[30-32] and the Brain Attack Coalition defined a set of criteria for constituting a primary stroke center.[33] Subsequent registries have confirmed the safety of treatment with intravenous t-PA in the community.[31,34]

When a patient such as this presents with symptoms of acute stroke, we must use all available information to determine whether there is still sufficient brain at risk to justify the hazards of thrombolytic treatment. Surrogates such as the time from the onset of symptoms and evidence of infarct progression on imaging help determine these risks. The Glasgow Coma Scale does not provide the information needed, since a patient with complete left hemiplegia, a left visual-field defect, and anosagnosia could still have a score of 15. The patient under discussion was not thought to be a favorable candidate for intravenous t-PA, since she had had symptoms in the preceding 24 hours, she had a high NIHSS at the scene, and the results of her neurologic assessment were pharmacologically obscured. It should be noted that any changes in pupil size or reactivity were not due to the use of neuromuscular blockade, since these agents do not alter the pupillary reflex.

The benefit of catheter-based thrombolysis is less well studied than that of intravenous thrombolysis. A randomized trial comparing prourokinase combined with low-dose intravenous heparin to low-dose heparin alone in patients with persistent occlusion of the middle cerebral artery[35] found that patients treated with prourokinase were more likely to have recanalization and

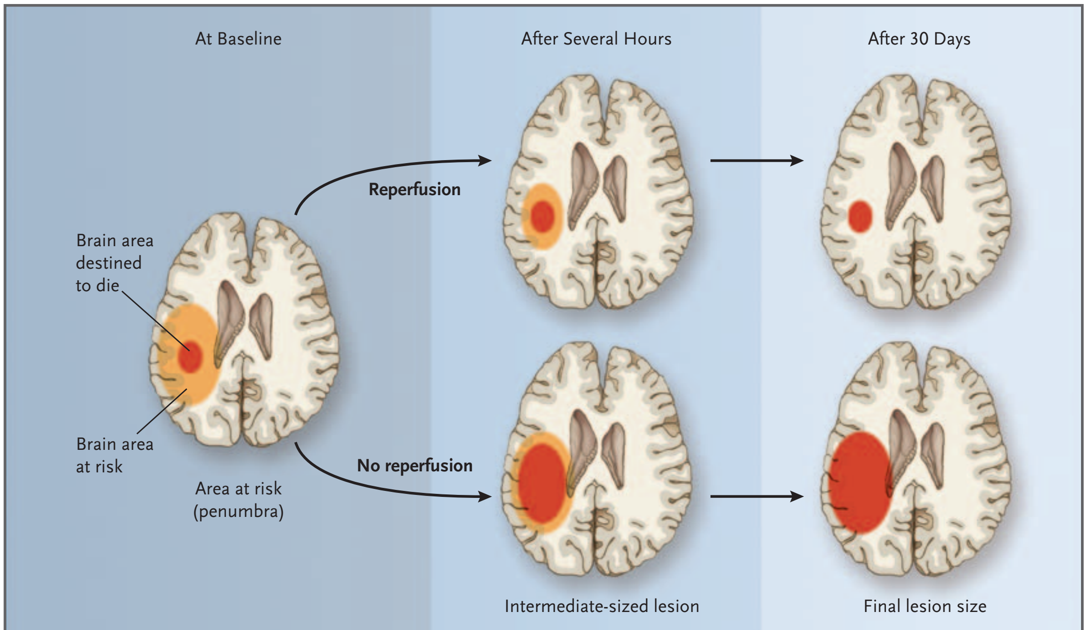

Figure 2. Representation of Penumbra in Acute Stroke.
The territory of the brain at risk for infarction is shown in yellow, and the brain destined to die is shown in red. The tissue shown in yellow represents potentially salvageable brain cells if reperfusion occurs rapidly.

to be independent three months later. Despite an increase in symptomatic intracerebral hemorrhage within 24 hours, the mortality rate was similar. In 2004, the Food and Drug Administration approved a mechanical embolectomy device for removing thrombus in patients who are ineligible or have no response to treatment with intravenous t-PA[36]; such an approach may offer some benefit in these patients.[37,38] The use of intraarterial fibrinolysis three to six hours after occlusion of the middle cerebral artery is considered a class II level B or C recommendation according to the American Heart Association[30,32] and should be done at an experienced stroke center with immediate access to cerebral angiography and interventional neuroradiology. The availability of intraarterial thrombolysis should not preclude the administration of intravenous t-PA in otherwise eligible patients.

Because of the large territory of brain at risk, the patient under discussion was thought to be a candidate for reperfusion therapy. The risks and benefits of catheter-based thrombolysis were discussed with the family, and they elected to proceed. A propofol infusion was initiated, and the patient was taken directly from CT to the interventional neuroradiology suite. Angiography confirmed the occlusion of the middle cerebral artery and showed that collateral blood flow through surface pial arteries from the anterior cerebral artery was helping to keep the cortex of the middle cerebral artery perfused. Intravenous eptifibatide was initiated (a bolus of 90 μg per kilogram was followed by an infusion of 0.5 μg per kilogram per minute) and was followed by intraarterial t-PA at 3:30 p.m. By 5:30 p.m., all vessels had been opened except for a distal branch of the middle cerebral artery supplying the frontal lobe. The patient was admitted to the neurology intensive care unit, and unenhanced CT of the head showed salvage of the entire cortical region at risk, with only deep gray-matter infarction.

Dr. Lev: Complete recanalization of the middle cerebral artery was achieved with the use of intraarterial thrombolysis within six hours after the onset of stroke. Follow-up unenhanced CT three days later showed complete recanalization of the middle cerebral artery, except for a small distal, frontal embolus in the artery (Fig. 3A). CT (Fig. 3B), diffusion-weighted imaging (Fig. 3C), and fluid-attenuated inversion recovery magnetic resonance imaging (MRI) (Fig. 3D) confirmed the presence of an infarct core at the right lenticular nucleus. A small distal right frontal cortical infarct was also apparent, attributable to the distal embolus in the middle cerebral artery.

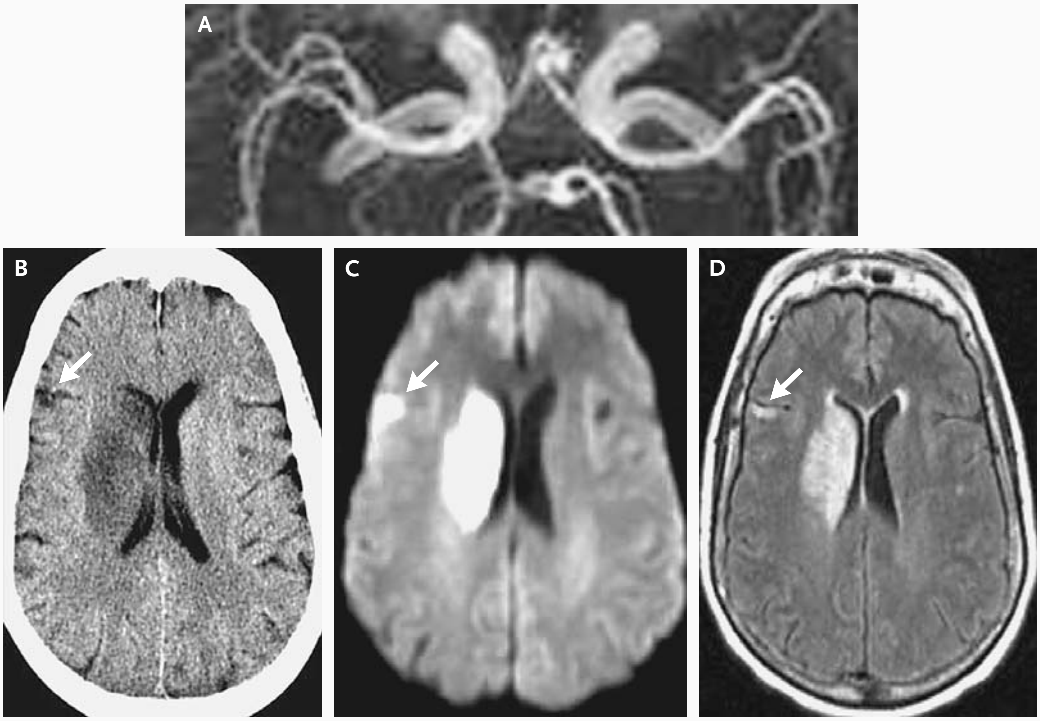

Figure 3. Imaging Studies Obtained Three Days after the Stroke.

An unenhanced three-dimensional time-of-flight magnetic resonance angiogram obtained three days after the stroke (Panel A) shows recanalization of the proximal right middle cerebral artery. A follow-up unenhanced CT obtained on day 3 (Panel B) shows a final infarct corresponding to the hypodensity seen on the admission CT shown in Figure 1D. An additional small right frontal cortical infarct is attributable to a tiny distal embolus that occurred after intraarterial thrombolysis (Panel B, arrow). The infarcted area is also shown on follow-up diffusion-weighted MRI (Panel C, arrow) and fluid-attenuated inversion recovery MRI (Panel D, arrow).

Dr. Schwamm: The patient had an excellent clinical outcome. No source of embolism was detected, and she was discharged on the seventh hospital day to inpatient acute care rehabilitation while receiving antithrombotic therapy for stroke prevention. At the time of discharge, she was alert and fully oriented, with fluent speech but some difficulty with naming. She had a left-sided facial droop and a very mild weakness of the left leg but could walk independently. By three months after the stroke, she had had a truly remarkable recovery, with a normal neurologic examination except for trouble reading difficult material, such as newspapers and textbooks. Four years later she had no neurologic impairment.

This case highlights the need for integrated, community-wide care for stroke.[39] In 2004, the Massachusetts Department of Public Health (DPH) implemented a hospital-based acute-stroke licensure program to support rapid evaluation of patients for possible intravenous t-PA therapy.[40,41] The system directs patients who have had stroke symptoms for no longer than two hours to nearby DPH-approved primary stroke service hospitals, with the use of telemedicine-enabled acute-stroke consultation[42] as needed to provide access to bedside neurologic expertise (see the video clip, available with the full text of this article at www.nejm.org).

Dr. Leslie W. Milne (Emergency Medicine): How do you decide between CT and MRI before you order intravenous t-PA or other therapy?

Dr. Schwamm: The published data on efficacy are based on the unenhanced CT. Treatment should begin as soon as the results of the examination, history taking, laboratory analyses, and unenhanced CT confirm a patient's eligibility. For sites considering catheter-based intervention, CT angiography provides rapid neurovascular assessment, but it is not available at many centers. MRI with diffusion-weighted and perfusion imaging may be useful in patients with normal findings on unenhanced CT if it can be done within 25 minutes after a patient's arrival.

Dr. James Gordon (Emergency Medicine): What is the current thinking about the use of thrombolysis for small-vessel as compared with large-vessel disease?

Dr. Schwamm: The National Institute of Neurological and Communication Disorders and Stroke study did not require patients to undergo vascular imaging before treatment, but there was no difference in effect between presumed small-vessel and large-vessel stroke.[43] Although many people have questioned the wisdom of using intravenous t-PA in small-vessel stroke because the outcome of natural recovery is presumed to be excellent, only 33 to 50 percent of the patients had this outcome at three months. In addition, many patients who did not receive intravenous t-PA because they were deemed to have mild or rapidly improving stroke are subsequently unable to be discharged home because they are not ambulatory.[43]

Dr. Nancy Lee Harris (Pathology): This patient lived in a suburb of Boston. Where did the helicopter land to pick her up?

Dr. Thomas: We have plotted landing zones near just about any conceivable area (i.e., a school field, a parking lot, or in the street). Ground transport is used from the home to the landing area.

Dr. David F. Brown (Emergency Medicine): Although this patient did very well, it took about an hour from the time the first EMS crew arrived to her arrival in our emergency department. The patient might have been transported by ground transportation to a local hospital with a stroke center much more rapidly and could have been treated with thrombolysis even more promptly than she was here. Do you envision that the numbers of stroke facilities will continue to grow throughout the state and throughout the country so that air transport will remain rare? Or are we heading toward a system of acute-stroke care that will be similar to that for patients with trauma, in which patients will be preferentially taken (by ground or by air) to a select group of large hospitals that will provide comprehensive stroke care?

Dr. Schwamm: The two models you just proposed are playing out differently in different parts of the country. In Massachusetts, the decision was made to emphasize primary stroke centers, a relatively low-level facility designation that would be available within a short distance of every patient in the Commonwealth, and to strengthen the connections of such hospitals to more comprehensive centers. The plan recognizes that air transport might be appropriate when you cannot reach a nearby stroke center or the nearest center is not currently capable (e.g., the CT scanner is offline).

ANATOMICAL DIAGNOSIS

Acute ischemic stroke.

Dr. Thomas reports having received consulting fees and grant support from MedWave and UCB Pharma. Dr. Schwamm reports having received consulting fees from Boston Scientific, CoAxia, and Cordis; the donation of equipment from PolyCom; lecture fees from Best Med; and grant support from AstraZeneca. Dr. Schwamm reports having reviewed medical records as an expert witness for cases of cerebrovascular disease. Dr. Lev reports having served as a speaker for GE Medical Systems and Bracco Diagnostics. No other potential conflict of interest relevant to this article was reported.

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