Objectives:

1) Describe the literature behind clinical decision making in acute ischemic stroke
2) Identify the potential uses of new imaging technologies in acute stroke management
3) Define the critical decision making behind treatment of intracerebral hemorrhage

Introduction

Acute stroke care is a multidisciplinary effort that has seen tremendous change in the past decade. The overall effort of treating stroke patients to optimize their outcome has experienced a few medical advances and a number of political/organizational advances. The most notable medical advances are reperfusion efforts for acute ischemic stroke as well as significant advances in imaging stroke of all types. The political/organizational advances include formalization of “Stroke Center” recognition as well as many efforts to mandate regionalization of stroke care. The sum of these medical and organizational advances, if implemented well, can significantly improve outcomes from stroke and represent the current state of the art.

Acute Stroke Care Treatment Advances

The era of reperfusion for acute ischemic stroke became a reality after the publication of the NINDS rt-PA study in the New England Journal of Medicine in December, 1995. Early in this process there were clearly multiple factors which led to controversy. The most focal criticisms of this proposed therapy were the “amount of data” upon which the FDA approval and subsequent advocacy for this treatment were based. In addition, multiple negative trials of thrombolysis for stroke called into question the wisdom of accepting a new therapy based on two combined trials with only 624 patients. In addition, a subsequent Cochrane Review similarly questioned the validity of thrombolysis in general for acute ischemic stroke.

Research done early in the evolution of acute reperfusion therapy for stroke demonstrated that patient selection and adherence to guidelines for this therapy are critical. This work, followed by a broad-based educational effort to reduce errors in patient treatment ultimately demonstrated that error reduction was possible and that the very concerning risk of hemorrhage in acute stroke therapy can be limited. It is clear that education, team communication and multidisciplinary input is required to optimize thrombolysis for acute stroke.

One study that was done during the height of this controversy is a well performed pooled analysis of all patients treated with t-PA for acute ischemic stroke. In this Lancet publication in 2004, all patients treated with t-PA for acute ischemic stroke within six hours from five large clinical trials were pooled and subsequently analyzed. In the methodology of a pooled analysis, individualized patient data from multiple trials is pooled together and subsequently analyzed. In this analysis, 2775 patients from over 300 hospitals and 18 countries randomized to t-PA or placebo for acute ischemic stroke within six hours were analyzed. Ultimately, this pooled analysis demonstrated that patients treated within 4.5 hours of acute ischemic stroke onset with t-PA have an improved outcome over patients not treated. This is true for each individual 90 minute increment from 0-90 minutes, 91-180 minutes, and in fact 181-270 minutes. It must be noted that beyond 4.5 hours patients treated with t-PA for acute ischemic stroke were found to actually do worse than placebo patients. Thus, there is clearly an inflection point based on time somewhere in the vicinity of the 4.5 hour region.
A significant change in the overall acceptance of thrombolysis for acute stroke came with the publication of “A Placebo Controlled Trial of Alteplase in Acute Ischemic Hemispheric Stroke Where Thrombolysis is Initiated Between 3 and 4.5 Hours After Stroke Onset.” This trial, also known as ECASS 3, was the first large thrombolytic trial in ischemic stroke in many years. The inclusion and exclusion criteria are similar to the NINDS rt-PA stroke trials with a few additional exclusions. The trial enrolled approximately 800 patients and was conducted in 15 countries. The final patient was enrolled in February, 2008. In the final results of this trial, patients treated with rt-PA were more likely to have a favorable clinical outcome than patients treated with placebo (52.4% vs. 43.2%; odds ratio, 1.34; 95% confidence interval [CI], 1.02 to 1.76; P=0.04). With the ECASS 3 trial’s positive result there was further weight to the argument that thrombolysis of acute ischemic stroke in the first few hours is beneficial. It also validated the findings of the pooled analysis of all previous rt-PA patients treated in acute stroke trials. This study has led many clinicians and stroke teams to expand their window for appropriately selected patients with acute stroke.

The sum of the literature to date has led to greater acceptance of the use of rt-PA in appropriately selected patients. It is clear that proper patient selection is necessary as the risk benefit ratio for thrombolytic therapy is predicated on choosing patients who clearly meet criteria for such treatment. It has also become evident that the time window may be as long as 4.5 hours for appropriately selected patients. As more clinicians become comfortable with this approach, a greater number of patients are offered the chance for reperfusion. Clearly, efficient delivery of intravenous thrombolysis by an organized and ready hospital team is one required element for state of the art for acute stroke care.

Parallel to the implementation and advances in intravenous thrombolytic therapy has been a sharp rise in the use of intra-arterial reperfusion therapies. This type of treatment was initiated in the mid 1990s with multiple significant inflection points. The first major evidence of increased use came with the FDA approval of the MERCI Retriever. The Merci Retrieval System is described by the maker as a “minimally invasive catheter-based system designed to retrieve and remove clots in patients experiencing acute ischemic stroke.” The Merci Retrievers are corkscrew-shaped products designed to remove blood clots from large vessels within the neurovasculature. The Merci Retriever was first cleared for human use in 2004 by the FDA. Since that time, the MERCI device has undergone a number of significant engineering changes making the device easier to direct and deploy. There now are a greater cadre of individuals and centers performing such treatments. This use has led to more opportunities to gain experience for new operators. Intra-arterial invasive treatments are now relatively common in large stroke centers. In addition, there has now been the approval of another instrument, the Penumbra device. This system uses a unique microcatheter and separator. Essentially this is a two pronged approach to break up and aspirate the clot and clear the vessel. This device received FDA clearance in 2008 and becoming more popular.

One recent and significant change which has increased the use of intra-arterial therapies came with the recent addition of a funding code which makes the practice more financially feasible. In 2006, the ICD-9 code 39.74 created a billing mechanism for “Endovascular removal of obstruction from head and neck vessel(s).” This dramatically increased the reimbursement potential for endovascular approaches to acute ischemic stroke.

Despite the enormous progress relative to the treatment of acute ischemic stroke, the therapeutic advances for intracerebral hemorrhage (ICH) have been relatively rare. Trials of surgical and medical interventions have as yet failed to substantially alter outcome. Blood pressure management parameters, based on expert consensus, have provided improved guidelines for emergency care. One important change in perception of ICH in the emergency setting is the realization that unlike supratentorial hemorrhage, cerebellar hemorrhages are necessarily surgical emergencies and must be treated by rapid evacuation of the clot by the neurosurgeon.

Management of aneurysm-based subarachnoid hemorrhage has improved in two aspects. First, the timing of interventions has clearly moved from delayed to acute. This does call upon the emergency department (ED) team to coordinate both diagnosis as well as very early referral to a high volume center for definitive securing of the ruptured aneurysm. Second, along...
with earlier therapy has come the rapid uptake of endovascular procedures to ameliorate many of the aneurysms which are responsible for bleeding. Clearly this area of stroke therapy has been substantially improved over the last decade.\(^7\)

Finally, in order to try to sharpen the decision-making of the clinician, imaging researchers have made considerable improvements in the diagnostic armamentarium for acute stroke. Currently in the United States, non-contrast head computer tomographic (CT) imaging remains the primary imaging modality for the initial evaluation of patients with suspected stroke.\(^8\) Lesions which might mimic acute ischemic stroke such as tumor, trauma, and of course intracerebral hemorrhage, can be often excluded by the non-contrast head CT. The availability and rapidity with which a head CT can be obtained make this a very useful tool for differentiating a possible acute ischemic stroke from other lesions. This modality, however, does not begin to optimize the imaging evaluation of an acute ischemic stroke patient. Two diagnostic approaches which are rapidly becoming more available to the emergency physician are computer tomographic angiography (CTA) and advanced techniques in magnetic resonance (MR) imaging such as MR diffusion imaging.

The modality CTA is becoming rapidly available based on the increased availability of late generation multi-slice CT scanners. With this technique, imaging of the entire intra and extra cranial circulation beginning at the aortic arch through the Circle of Willis can be performed in less than 20 seconds. Individuals trained in reading these scans can find stenoses or occlusion of vessels immediately based on source imaging, and within just minutes' reconstruction of such imaging, can provide spectacular views of the arteries in question. Many advanced centers are beginning to use this technique in all acute stroke patients as many stroke experts believe this adds enough clinical information to merit initial acquisition of CTA at the time of presentation.\(^9\) It is quite easy to imagine how the patient with questionable symptoms causing angst for the provider could be differentiated based on the finding or absence of a significant intracerebral occlusion. One obvious downside to this technique is the requirement of the administration of contrast. The availability of point-of-care creatinine testing could diminish the patients receiving such a test who are at risk for contrast induced nephropathy. In series to date, the incidences of such nephropathy have been quite low.\(^10\)

Similar in value to the emergency physician to CTA are advanced MR images. While most centers cannot obtain MR imaging as rapidly as they do CT, there are a number of clinical scenarios in which the extra time required to obtain an MR image would have clinical merit. Specifically, the availability of MR diffusion imaging can dramatically alter care. Diffusion weighted MRI is based on the principle that random motion of water molecules in tissue can be measured and quantified. In the setting of acute ischemic stroke, ion pumps in the membranes of injured cells begin to fail. This leads to an acute increase in intracellular water in those affected cells. This difference in water content and water diffusion between affected cells and unaffected cells can be measured. Due to sophisticated programming, the affected tissue “lights up” on the diffusion images. These MR scans can be some of the most dramatic images in the management of acute ischemic stroke patients. Clinicians evaluating challenging patients can now differentiate between those who actually have an acute ischemic event versus those who do not. Such tests are particularly valuable in patients in whom complex migraine versus acute ischemic stroke must be differentiated. It should be noted that all MR imaging is alike. A full brain MRI can take up to an hour. The acquisition of MR diffusion takes less than 10 minutes. Therefore, the actual clinical determination of ischemic stroke can be performed in the first 10 minutes of MR imaging.\(^11\)

It is clear, therefore, that rapidly available imaging in the hands of skilled readers can significantly improve the diagnostic ability of the acute stroke team. Such advances have become standard practice in the most advanced stroke centers and represent the state of the art in current acute stroke management.

Organizational and Political Advances

One of the most important organizational changes in stroke care is based on the publication of the Brain Attack Coalition's Recommendations for the Establishment of Primary Stroke Centers. This was an effort to respond to the marked variability and at times unavailability of coordinated stroke care. In describing the situation which exists for stroke care the authors quoted research that documents 66% of hospitals do not have defined stroke protocols, and 82% lack a rapid identification system for patients experiencing acute stroke. Citing the experience, and documented success, of trauma centers in organizing and providing care for a disease with significant time-dependence, the authors proposed it is reasonable to explore the “center” concept for acute stroke. They also proposed, like the trauma system, there should be more than one “level” of stroke care center, proposing a two tier system with the elements being the “primary stroke center” and the “comprehensive stroke center.”\(^12\)
In the primary stroke center paper, the authors outline and detail the essential elements of a “Primary Stroke Center.” The Key elements of primary stroke centers include acute stroke teams, an integrated emergency response system, written care protocols and a “stroke unit”. Important support services include availability and interpretation of computed tomography scans 24 hours per day and rapid laboratory testing. Administrative support, strong leadership, and continuing education are also important elements for stroke centers. The authors believe that the adoption of these recommendations may increase the use of appropriate diagnostic and therapeutic modalities and reduce post-stroke complications.

Along with the stroke center efforts have been a number of political correlates, most commonly at the state level, which have mandated efforts to improve stroke care. Additional efforts have included an Institute of Medicine conference designed to improve regionalization of care including acute stroke care. Such efforts have concentrated on getting the right patient to the right level of care at the right time. This has significant implications for hospitals along the continuum of stroke capabilities as these institutions will be tasked with keeping the patients which are appropriate for their level of care and transferring those patients who are not to a more sophisticated stroke center.

**Conclusion**

In summary, the current state of the art for acute stroke care requires a multi-disciplinary team ready to make appropriate diagnostic and treatment decisions. These decisions require team communication and experienced clinicians who can accurately and rapidly determine when to employ thrombolytic therapy and which route to use. It requires advanced imaging to be both available quickly and read by skilled diagnostic imaging experts and stroke clinicians. It also requires involvement of the greater health care community to ensure that the right patients are getting to the right level of care at the right time.

**References**