MANAGEMENT OF ACUTE ISCHEMIC STROKE

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Case report

A 44-year-old right-handed woman presented to the ER with receptive aphasia and right sided upper extremity hemiparesis (1/5). Time of onset was unknown. BMI is 42. Past medical history is notable for tobacco use and hyperlipidemia. Medications include Lipitor. NIHSS is 22. CT scan (Figure 1) was normal (ASPECT Score 10). Catheter angiography revealed a left cervical ICA occlusion and a left MCA M1 large vessel occlusion (Figure 2).

CT BRAIN IN ER

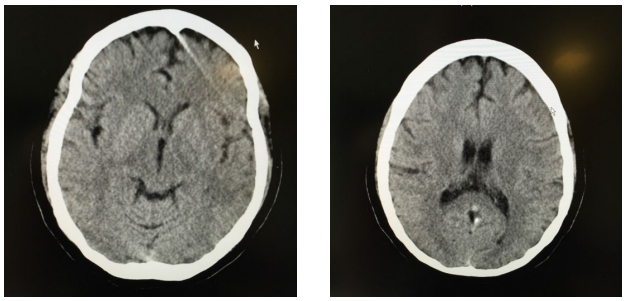

Figure 1: Normal CT upon presentation in the ER
(ASPECT Score 10)

Revascularization of the left MCA was carried out using a Solitaire thrombectomy device (Medtronic, Minneapolis, MN). Figure 3 shows the microcatheter positioned across the MCA occlusion. Figure 4 shows the microcatheter, Solitaire device and extracted thrombus. Figure 5 shows the re-opened left MCA. The patient underwent an MRI 24 hours later showing a left basal ganglia infarct but no changes in the distal left MCA territories (Figure 6).

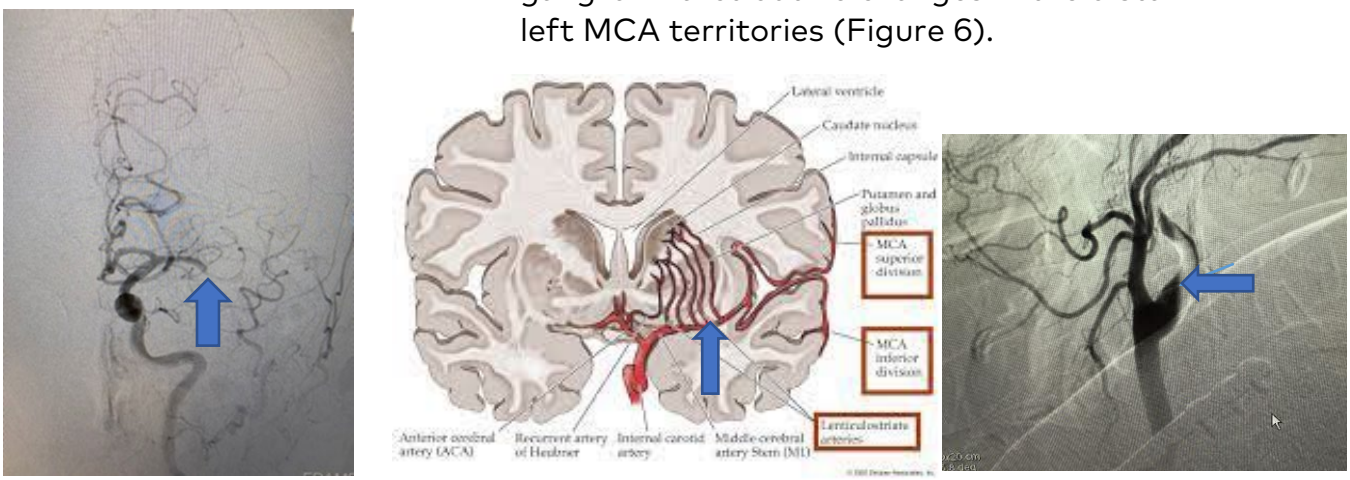

Figure 2: Angiogram showing left ICA occlusion and left MCA occlusion. The left diagram shows the location of the MCA occlusion (blue arrows)

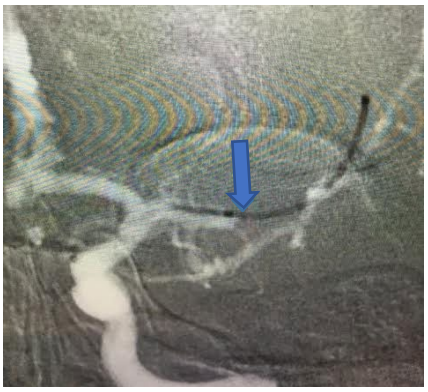

Figure 3: Angiographic image with the microcatheter positioned distal to the MCA occlusion (through the thrombus). The blue arrow points to the microcatheter in the MCA.

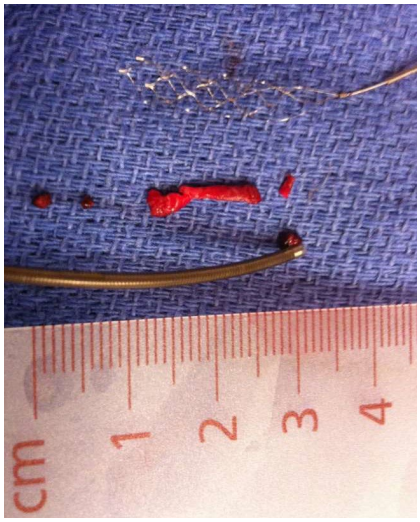

Figure 4: Microcatheter, Solitaire Thrombectomy Device, and extracted MCA thrombus.

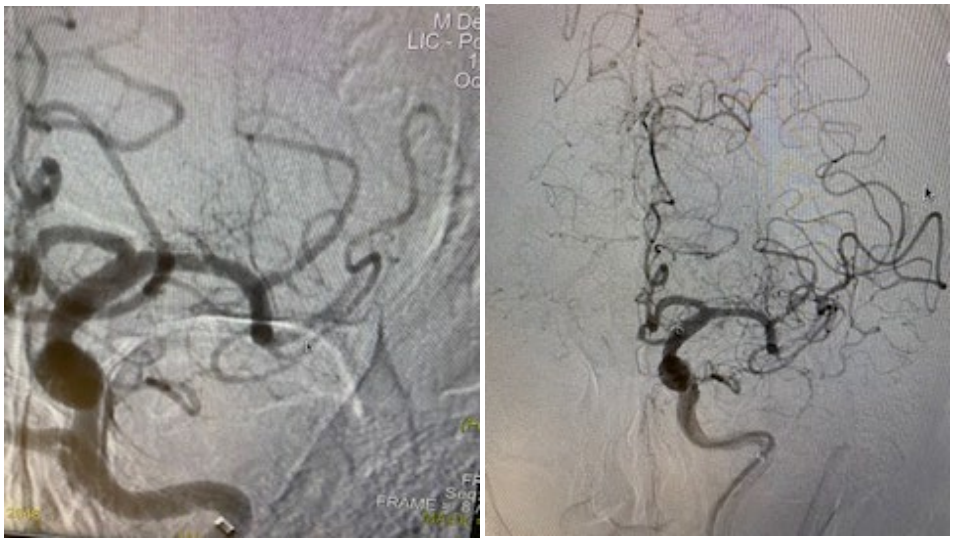

Figure 5: These images show the left MCA filling normally after the thrombus shown in Figure 4 was removed.

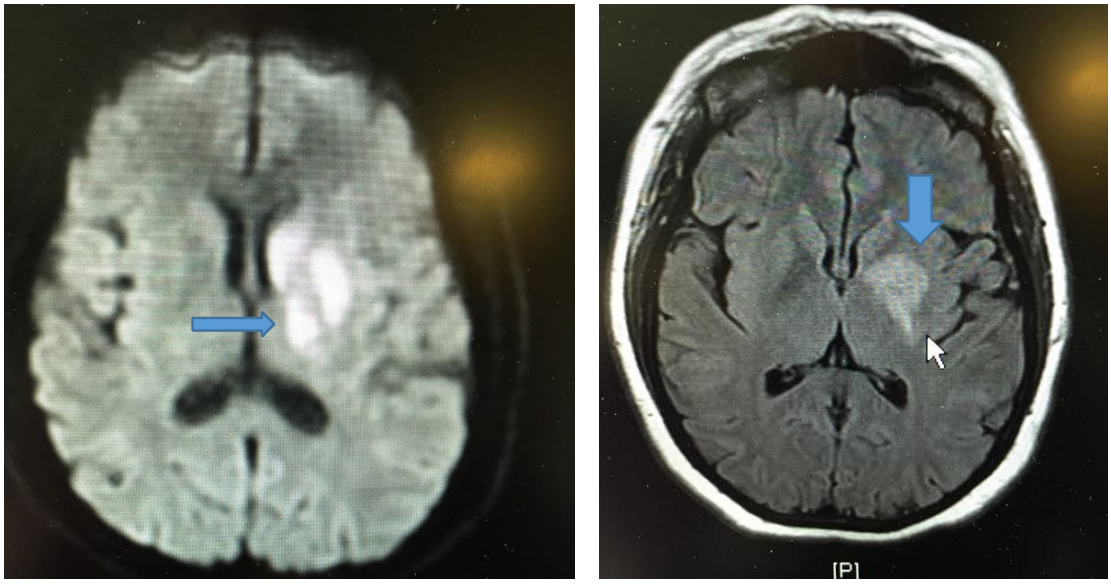

Figure 6: MRI 24 hours after the procedure showing basal ganglia stroke but no distal MCA territory ischemic changes.

The patient was discharged home 7 days later on 81 mg ASA per day with normal speech and 4/5 left upper extremity strength. Final work up revealed a heterozygous prothrombin gene variant mutation (hypercoagulable state).

Definitions

Stroke is a condition manifested by rapidly developing clinical signs of focal or global disturbance of cerebral function with symptoms lasting 24 hours or longer. This malady can include ischemic and hemorrhagic infarction, intracerebral hemorrhage and subarachnoid hemorrhage (SAH).

In adults 80-85% of strokes are ischemic while in children, 55% of strokes are ischemic.

Transient ischemic attack (TIA) defines clinical signs of focal or global disturbance of cerebral function that is related to reduced blood flow to the brain that lasts less than 24 hours.

This Topic Review will focus exclusively on ischemic stroke.

Disease Impact

Stroke is the number one cause of disability among adults in the United States with 795,000 Americans affected per year (1 stroke every 40 seconds). Stroke is a major cause of death with 128,000 mortalities per year.

Basic Physiology

The brain contains 2% of the total body weight yet, because of its high metabolic activity, it receives 20% of the cardiac output. Normal cerebral blood flow (CBF) is 50-65 cc/100g brain/minute. Brain perfusion is not only affected by cardiac output but by intracranial pressure.

As intracranial pressure rises, it becomes more difficult to perfuse the brain normally. This perfusion of the brain is measured by the cerebral perfusion pressure (CPP) which is calculated using the equation: CPP = Mean Arterial Blood Pressure – Intracranial Pressure.

One can see from this equation that if mean arterial pressure drops or if intracranial pressure rises, CPP will drop. It follows, therefore that if CPP drops then CBF can drop as well.

The brain tries to maintain CBF, and by dilating and constricting the arteries of the brain, the body can keep CBF constant over a range of CPP ranging between 60- and 140-mm Hg. Once CPP drops below 60 mm Hg, however, the brain can no longer maintain adequate blood flow to the brain.

- Once CBF drops below 20cc/100g brain/min brain dysfunction ensues.
- Once CBF drops below 15-18cc/100g brain/min EEG changes are seen.
- Once CBF drops below 8-10 cc/100g brain/minute neurons begin to die and stroke occurs.

Etiology of Acute Ischemic Strokes

For the purposes of this review on acute ischemic stroke we will focus on thromboembolic and occlusive mechanisms that can lead to reductions in CBF. These two physiologic events lead to reduction in CBF and a variety

of symptoms that depend upon the affected intracranial arteries and the cerebral territories that they perfuse. The potential underlying causes for such events such as carotid stenosis, atrial fibrillation, atherosclerotic disease, metabolic disease, patent foramen ovale (PFO) with paradoxical emboli, atrial myxoma, cardiac valvular disease, hypercoagulable states, inherited and acquired thrombophilia, drug use and vasculopathy will be elaborated upon in future newsletters.

Patient Evaluation

No matter what the etiology is for an acute thromboembolic or occlusive stroke, the emergent evaluation remains almost uniform. This uniformity ensures rapid triage and proper intervention when possible.

Step 1: All patients suspected of suffering a stroke should undergo an expeditious history and physical.

History should include determination of the last known time the patient was seen to be normal or at baseline. This information will define the official "time of onset". Time of onset (TOS) will in turn help define potential future therapies.

In addition to TOS, it is imperative that first responders and ER personnel note past medical history (cardiac history, stroke history), past surgical history, pregnancy status, other neurologic diseases, and current medications. It is extremely important to determine if the patient is on any antiplatelet or anticoagulant medications as these can affect the use of certain stroke therapies.

While a detailed physical examination can be useful, this can consume precious minutes. For that reason, the physical examination, aside from vital signs, can be initially replaced by obtaining a National Institute of Health Stroke Score (NIHSS).

This scoring system may seem intimidating at first, however, by using readily free downloadable applications that can be placed onto a smart device/phone such as NeuroToolkit, Stroke Scale and MDCalc, the medical provider can rapidly and consistently determine a patient's neurologic level of function.

The NIHSS, like the TOS, is an important component of the initial evaluation that helps select patients for various treatment algorithms.

The reliable inter-observer reliability of the NIHSS also provides the ability to follow a patient's examination over time to check for improvement or decline in neurologic function. The NIHSS point system ranges from 0–42.

A score of 0 denotes a normal examination, 1-4 reflects minor symptoms, 5-15 indicates moderate symptoms, 16-20 represents moderate to severe symptoms and 21-42 marks a severe stroke.

NIHSS can help predict outcomes. Left untreated, an NIHSS >16 portends the strong possibility of death while NIHSS <6 indicates a strong possibility of a good recovery. An increase in 1 point in a patient's NIHSS decreases the likelihood of an excellent outcome by over 10%.

Step 1 can be completed in less than 5 minutes and can be obtained in the field as easily as it can in the hospital.

Step 2: All patients suspected of having any intracranial pathology should undergo immediate head CT scan to determine whether there has been an intracranial hemorrhage, or an intracranial mass (tumor) exists.

The CT scan may also demonstrate evidence for ischemic tissue. If the CT scan reveals ischemic changes, then the radiologist, neurologist or neurosurgeon should determine the Alberta Stroke Program Early CT Score (ASPECT Score).

This 10-point scoring system quantifies the volume of ischemic brain seen on CT scan. A score of 10 denotes no evidence on CT for ischemia (ischemia might be present, but it may be too early for the radiographic changes to be seen on CT).

An ASPECT Score <7 predicts worse functional outcome at 3 months as well as the increased risk for developing delayed intracranial hemorrhage into the damaged brain tissue.

Nevertheless, many practitioners support aggressive endovascular treatment of patients with low ASPECT scores in an attempt to improve outcomes in these gravely compromised individuals.

CT arteriography performed at the same time as the CT can be useful.

This study rarely adds significant time to the plain CT imaging and can quickly determine if a patient harbors a large vessel occlusion (LVO) that is defined as an ICA or MCA thromboembolism.

By determining the presence or lack thereof of an LVO using CTA, a decision can be made as to whether emergent cerebral catheter arteriography and thrombectomy/thrombolysis/stenting is warranted.

Some practitioners choose to reserve CTA for evenings or weekends because the CTA can be performed while the treatment team is traveling to the hospitals. In these situations, CTA will not delay definitive diagnosis and treatment. These practitioners may choose to avoid CTA during regular hours in an effort to more quickly definitively diagnose and treat an LVO.

CT perfusion (CTP) is often used to help select for patients that will more likely favorably respond to revascularization. Data provided by CTP can also help identify patients who are at increased risk for hemorrhagic conversion of the infarcted tissue following arterial recanalization.

This modality provides the following data points: (1) volume of brain tissue has already died and will not recover if blood flow is reestablished (aka: Core); (2) volume of brain tissue that suffers from a reduction in blood flow, but which could recover if blood were reestablished (aka: Penumbra).

Patients who are best suited to benefit from thrombectomy revascularization are those who have a Core that measures less than 70-100 cc, a Penumbra:Core ratio of >1.8, and a Penumbra to Core mismatch (Penumbra volume minus Core Volume) that is greater than 15 cc.

While MRI can be helpful for evaluation of acute strokes, the time it takes to obtain and interpret such studies generally outweighs the benefits of the information these studies provide and as of this time, this modality is not routinely indicated nor standard of care in most situations.

Such imaging may be useful for patients presenting for treatment beyond the 12-hour window to help guide decision making, but this is considered on a case by case basis.

Patient Treatment: Intravenous Thrombolytics

- Intravenous Tissue Plasminogen Activator
    - iv-tPA; Alteplase
    - iv-TNK; Tenecteplase

When patients present within 4.5 hours of onset of stroke symptoms (within 4.5 hours of last known normal) they are generally eligible for iv-tPA if their NIHSS exceeds 4 (0.6-0.9 mg/kg not to exceed 90 mg total dose infused over 90 minutes with 10% administered as a bolus over minute 1).

This recombinant drug cleaves plasminogen into the protease plasmin that in turn degrades Fibrin. Polymerized Fibrin normally combines with platelets to form a hemostatic clot; hence degradation of Fibrin can degrade thrombus and reopen an occluded vessel.

Absolute and relative contraindications to iv-tPA administration are numerous. Once again these can be retrieved on a smart device/phone using an application such as Stroke pocketcards. The use of iv-tPA was approved by the FDA in 1996 following published study results in 1995 (NEJM. 333:1581-1588, 1995).

A follow-up study published in 2016 suggested that reducing the dose to 0.6 mg/kg might yield equivalent results to 0.9m/kg while reducing the risks of intracerebral hemorrhage from 2.1% to 1% (NEJM. 374:2313-2323, 2016).

The use of iv-tPA beyond the 4.5-hour window from last known normal has been investigated in the EXTEND Trial. The results of this study were reported at the International Stroke Conference in February 2019. This study used CT and MR perfusion to determine if there was a patient population that might benefit from the administration of iv-tPA in the >4.5-hour period.

Results were favorable. EXTEND may ultimately lead to changes in the indications for iv-tPA administration and might increase the use of perfusion studies in certain situations.

Endovascular Therapy for LVO

Endovascular (mechanical and suction thrombectomy, super selective intra-arterial tPA infusion) treatment of acute LVO stroke is of interest because of two factors.

- The first is that recanalization rates for iv-tPA administered within 4.5 hours of last known normal are only 5-14% for ICA occlusions and 20-44% for MCA occlusions.
- The second is that the degree of recanalization is the most important determinant of the size of infarct volume (less recanalization leads to greater infarct volume and worse outcomes).

As a result of these considerations, physicians have looked for ways to increase treatment efficacy.

The MR CLEAN Study (NEJM. 372:11-20, 2015) evaluated patients treated using thrombectomy and iv-tPA as opposed to iv-tPA alone.

This study showed that in patients treated using combined therapy there was no difference in mortality, 71% improvement in good neurologic outcomes, and no residual occlusion in 75% of treated vessels.

A subgroup analysis later showed benefit to combined therapy in patients with ASPECTS >5 (Lancet. 15:685. 2016).

Additional studies such as SWIFT PRIME, EXTEND IA, REVASCAT, AND ESCAPE compared iv-tPA alone to iv-tPA plus thrombectomy. These investigations revealed that when combination therapy was used from 4.5 – 12 hours from last known normal time of onset, outcomes were improved over those following iv-tPA alone without any increase in morbidity or mortality.

The above studies investigated the combined use of iv-tPA and endovascular thrombectomy and demonstrated clear benefits.

What about patients who are not eligible for iv-tPA? Can these individuals be helped using endovascular therapy alone?

The HERMES Study addressed these questions showing benefits to thrombectomy alone, thus giving hope to another subgroup of patients (Lancet. 387 (10029):1723-1731, April 2016).

In 2017, the DAWN Study (NEJM. 378:11-21, 2018) gave hope to patients with significant deficits and small infarct volumes on CT ("Mismatch between Deficit and Infarct") presenting 6-24 hours from last known normal.

In this investigation, patients with small infarct volumes (mean volume 7.6 ml; range 2-18 ml) and moderate to severe NIHSS (median 17; range 13-21) were randomly assigned to undergo either standard care for strokes that presented beyond the tPA window or thrombectomy.

Ninety-day functional independence was 49% in the thrombectomy group vs. 13% in the control group and mortality at 90 days was 19% in the thrombectomy group vs 18% in the control group. Symptomatic intracranial hemorrhage was less than 7% in both groups (no statistical difference).

By extending the therapeutic window to 24 hours, DAWN has expanded the pool of individuals who may benefit from aggressive treatment.

Posterior Circulation Acute Strokes

There are no clear recommendations for the management of posterior circulation LVO such as those involving the basilar artery. Symptomatic occlusions are evaluated on a case-by-case basis.

Revascularization attempts are indicated in most cases that do not show large areas of brainstem ischemia due to the >90% risk of symptom progression and death from such arteriopathy.

All treatments are considered off label and at the discretion of the treating physician in consultation with the patient's family when possible.

Decompressive Craniectomy

It is not uncommon for patients with middle cerebral artery or posterior circulation strokes to develop severe brain swelling secondary to brain tissue infarction and a subsequent associated cytotoxic edema (resistant to steroids and poorly responsive to osmotic agents).

If severe, brain swelling within a closed volume (skull) leads to herniation, destruction of remaining functional tissue, and severe disability/death.

Select patients may benefit from prophylactic or early decompressive craniectomy and dural opening/expansion.

This procedure removes a portion of the skull, opens the dura (increases the cranial vault volume) and closes the scalp so that brain can swell outward thus reducing the likelihood of herniation syndromes. Once swelling has subsided, the previously removed portion of the skull can be replaced with either the original bone or with an artificial substitute made from titanium or a hardened polymer.

Patients who benefit the most from decompressive craniectomy are generally those who are younger than 50 years of age and who suffer from non-dominant hemisphere or cerebellar ischemic events. Treating patients prior to the onset of symptomatic herniation is desirable.

Conclusion

Acute management of ischemic stroke has advanced significantly over the last decade. Study data and improvements in technology have made it now possible to intervene on patients who were previously relegated to a course of watchful waiting. Rapid referral of such patients to centers of excellence is imperative and crucial to a patient's effective treatment and recovery.

If you would like to learn more about the effective treatment and care of ischemic stroke, please contact Dr. Michael Horowitz at HCA Florida First Coast Neurosurgery at (904) 276-7336.