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Evidence-based summaries of the latest clinical neurology research

SPECIAL ISSUE: STROKE

Proceedings From the International Stroke Conference, Honolulu, February 2019

By Matthew E. Fink, MD, Editor

Feil Professor and Chairman, Department of Neurology, and Assistant Dean of Clinical Affairs, Weill Cornell Medical College; Neurologist-in-Chief, New York Presbyterian Hospital

Dr. Fink reports no financial relationships relevant to this field of study.

Message from the editor: The following reviews of studies presented at the 2019 International Stroke Conference were written after my personal attendance at the presentations, followed by review of the simultaneous publications in The New England Journal of Medicine *and* The Lancet. *All comments and opinions are solely those of this editor.*

Treatment of Factor Xa Inhibitor-Related Major Bleeding With Andexanet (LB7)

SOURCE: Connolly SJ, Crowther M, Eikelboom JW, et al. Full study report of andexanet alfa for bleeding associated with Factor Xa inhibitors. Concurrently published in *N Engl J Med* 2019; Feb 7. doi:10.1056/NEJMoa1814051.

Factor Xa inhibitors, such as apixaban and rivaroxaban, are used widely for preventing thromboembolism in patients with atrial fibrillation, deep venous thrombosis, and pulmonary embolism. However, when there is a serious bleeding complication, particularly intracranial hemorrhage, there have been limited treatments available to reverse the anticoagulant effects of these medications.

Andexanet is a recombinant coagulation Factor Xa and is designed to rapidly neutralize Factor Xa inhibitors at times of acute bleeding. Connolly and colleagues from the University of Texas studied an adult population presenting with major bleeding occurring within 18 hours of their last dose of apixaban, enoxiban, enoxaparin, or rivaroxaban. Patients received either a low dose (400 mg bolus plus 4 mg/min infusion for two

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[INSIDE]

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hours) or high dose (800 mg bolus plus 8 mg/min infusion for two hours) of andexanet, depending on the timing and dose of the specific anticoagulant agent that the patient was taking. The primary outcomes were change from baseline in anti-Xa activity and the rate of effective hemostasis within 12 hours. Hemostasis was determined in each patient through evaluation by an independent committee that reviewed the clinical case records. Patients were included in the evaluation if the committee considered the bleeding serious and if baseline anti-Xa activity was greater than 75 ng/mL. Safety outcomes included death and thrombotic events at 30 days following treatment with andexanet.

The investigators enrolled 352 patients from 76 sites worldwide from 2015 through 2018. The mean time from last dose taken of a Factor Xa inhibitor to andexanet administration was 12 hours. Serious bleeding was localized to the intracranial compartment in 64% of patients — intraparenchymal bleeding into the brain (ICH) comprised 46%, subdural bleeding 28%, and subarachnoid bleeding in 15%. Serious gastrointestinal (GI) bleeding occurred in 26% of patients. Mean age was 77 years. Indications for treatment with Factor Xa inhibitors were atrial fibrillation in 80% and venous thromboembolism in 17%. In the study, 194 patients were taking apixaban, 128 were taking rivaroxaban, 20 were taking enoxaparin, and 10 were taking edoxaban.

A total of 249 cases of bleeding were adjudicated, and treatment with andexanet resulted in excellent or good hemostasis in 204 patients (82%). In 71 patients with nontraumatic, intraparenchymal brain hemorrhages, 56 had volume expansion of < 35% from baseline in one hour. Of these, 55 of 56 had no additional hematoma expansion at 12 hours. The safety profile was excellent, but 34 patients (9.7%) had at least one thrombotic event within 30 days — seven patients had myocardial infarction, 14 had ischemic stroke, and 13 had deep vein thrombosis. All thrombotic events occurred before anticoagulation was restarted. Thirty-day mortality was 15% for patients with intracranial hemorrhage and 11.1% for patients with GI hemorrhage.

Andexanet rapidly reversed anti-Factor Xa activity and resulted in effective hemostasis and a 30-day mortality from ICH of 15%, well below what has occurred in historical control groups. ■

Dual Antiplatelet Therapy With Cilostazol for Secondary Stroke Prevention (LB3)

SOURCE: Toyoda K, et al. Dual antiplatelet therapy using cilostazol for high-risk ischemic stroke: The cilostazol stroke prevention study for antiplatelet combination (CSPS.com). ISC 2019.

In previous studies, dual antiplatelet therapy with aspirin and clopidogrel was shown to reduce early recurrence of ischemic stroke, with short-term benefit and a long-term risk of major bleeding. Cilostazol has been used to reduce the risk of recurrent stroke with a low bleeding risk and is safe for long-term use. Toyoda and colleagues from Osaka, Japan, reported on a multicenter, open-label trial in which high-risk patients with benign cardioembolic ischemic stroke identified on MRI were assigned to receive aspirin or clopidogrel alone, or a combination of cilostazol 100 mg twice a day with aspirin or clopidogrel for secondary stroke prevention. High-risk patients were defined as meeting one or more of the following criteria: greater than 50% stenosis of a major intracranial or extracranial artery and two or more vascular risk factors. The primary outcome was the first recurrence of an ischemic stroke. Safety outcomes included severe or life-threatening bleeding.

Following enrollment, 1,839 patients were available for analysis, with 756 taking aspirin and 1,083 taking clopidogrel. Ischemic stroke occurred in 29 of 913 patients (3.2%) with dual therapy including cilostazol and in 64 of 926 patients (6.9%) on monotherapy during a median follow-up of 17 months (P = 0.001). Severe bleeding occurred in 0.9% of patients on dual therapy and 1.4% of patients on monotherapy (P = 0.354). The investigators concluded that patients treated with dual antiplatelet therapy combining cilostazol with either aspirin or clopidogrel had a lower risk of ischemic stroke recurrence and a similar risk of significant bleeding compared to patients treated with aspirin or clopidogrel alone. ■

Treatment of Intracerebral Hemorrhage With Deferoxamine (LB22)

SOURCE: Selim M. Intracerebral Hemorrhage Deferoxamine (iDEF) trial results. Presented at ISC 2019.

It is postulated that secondary neuronal injury following intracerebral hemorrhage (ICH) is caused by release of iron from hemolyzed erythrocytes. Deferoxamine is an iron chelator shown to have neuroprotective effects and improves recovery in animal models of ICH.

Selim and colleagues from Boston performed a Phase II clinical trial to determine if use of deferoxamine showed significant benefits to justify a Phase III trial. This was a multicenter, double-blind, randomized, placebo-controlled futility trial with an intention-to-treat analysis. The investigators randomized 294 patients with spontaneous supratentorial ICH to receive either deferoxamine 32 mg/kg/day or saline placebo given by intravenous infusion for three consecutive days. Treatment was started within 24 hours of ICH onset, and patients were followed for six months. Subjects were evaluated by the modified Rankin scale (mRS) and compared to the placebo group at three and six months. Safety endpoints included all adverse events until day 7 or discharge from the hospital. All other adverse events were recorded through 90 days.

A futility analysis was performed based on a primary hypothesis that the difference in good outcome proportions, as defined by the mRS at 90 days, is less than 12% in favor of deferoxamine treatment. At that point, it would be futile to move this treatment into Phase III evaluation. The primary results of the study showed that 34.3% of the deferoxamine-treated group and 32.9% of the placebo-treated group achieved an mRS score of 0-2, reaching an absolute risk difference of 0.6%. This result indicated that it would be futile to proceed with a Phase III trial. In addition, mortality at 180 days was 8.3% in the deferoxamine-treated group compared to 8.2% in the placebo group. ■

Intensive Control of Hypertension During and After Thrombolysis for Ischemic Stroke (LB6)

SOURCE: Anderson C, Robinson T; ENCHANTED Investigators. Main results of the enhanced control of hypertension and thrombolysis stroke study (enchanted) of the early intensive blood pressure control after thrombolysis. ISC 2019.

High systolic blood pressure > 185 mmHg is a contraindication to thrombolysis after acute ischemic stroke and is also avoided following successful thrombolysis to prevent intracerebral hemorrhage (ICH). Anderson and colleagues from Sydney, Australia, performed an international, multicenter, prospective, open-label, blinded trial. They randomly assigned thrombolysis-eligible patients with acute ischemic stroke < 6 hours of onset to intensive blood pressure management to attain a systolic blood pressure of 130-140 mmHg within one hour or to guideline-recommended blood pressure treatment to maintain systolic blood pressure < 180 mmHg, maintained over 72 hours. Choice of specific agents to treat hypertension were left to the discretion of the local treating physicians. The primary outcome was a comparison of modified Rankin scale (mRS) scores at 90 days, and safety outcomes were any intracranial hemorrhage diagnosed by standard criteria and central adjudication. Secondary outcomes included good recovery based on a mRS score of 0-1.

The investigators recruited and randomized 2,227 patients from 2012 until 2018, and 99% were followed and evaluated at 90 days. Median age of both groups was 67 years. Sixty-five percent of patients were Chinese, and 74% had Asian ethnicity. NIH stroke scores were similar in both groups. All patients were treated with alteplase, but at 67% of the standard dose, as part of a trial that also looked at modified dosage of thrombolysis. Comparison of the two groups showed an unadjusted ordinal shift of mRS scores with intensive blood pressure lowering, but the differences were not significant. There were no significant differences in functional outcome or mortality. There was a lower rate of intracranial hemorrhage in the intensive treatment group, 14.8% vs. 18.7% ($P = 0.0137$).

The investigators concluded that intensive lowering of blood pressure to < 140 mmHg was not superior to guideline-recommended blood pressure lowering to < 180 mmHg for primary disability outcomes. Intensive lowering of blood pressure was found to be safe with respect to outcomes, and there was significant evidence for a lower risk of ICH following thrombolysis in patients treated with intensive blood pressure reduction. It is difficult to know if the findings can be generalized, since most participants in the study were from China and Asia, and the etiology of ischemic stroke and ICH may be different in this population compared to other ethnic groups. ■

Minimally Invasive Surgery for Intracerebral Hemorrhage – MISTIE III Results (LB4)

SOURCE: Hanley DF, Zuccarello M, Awad IA, et al; for the MISTIE 3 investigators. MISTIE 3 trial results. Concurrently published in *Lancet* 2019; Feb. 7.

The MISTIE (Minimally Invasive Surgery Plus Rt-PA for ICH Evacuation Phase III) investigators used an experimental protocol that involves placement of a catheter into an intracerebral blood clot with enhanced

removal by repeated infusion of alteplase into the clot followed by aspiration over a three-day period. After 20 years of early-phase studies, the results of a Phase III trial were reported by Hanley and colleagues from Johns Hopkins University. The primary outcome measure was a comparison of patients who had modified Rankin scale (mRS) score of 0-3 vs. mRS score of 4-6 at 365 days after ICH.

The investigators randomized 499 subjects from 74 sites to the catheter aspiration procedure followed by alteplase irrigation or best medical therapy. The population was 61% male with an average age of 61 years. Sixty-two percent of the hemorrhages were in the basal ganglia and 38% were lobar. At presentation, the clot sizes averaged 44 mL with 6 mL of intraventricular hemorrhage. Mean Glasgow Coma Scores were 11. Age, Glasgow Coma Score, clot size, intraventricular hemorrhage volume, and patients who underwent withdrawal-of-care were not different between the groups. The protocol-defined surgical goal was to reduce the volume of ICH to < 15 mL, and this occurred in 59% of MISTIE patients. MISTIE vs. medical treatment was safe, with 30-day mortality of 9% vs. 15%, rebleeding rates of 3% vs. 3%, and infection rates of 1% vs. 0%. The primary endpoint, mRS score of 0-3 vs. 4-6 at 365 days, demonstrated a 3% difference favoring MISTIE patients, but this difference was not statistically significant. A mortality difference at one year of 6% vs. 8% occurred in favor of MISTIE patients, with an adjusted hazard ratio of 0.70 ($P = 0.03$). Successful ICH removal correlated with improved outcomes.

The investigators concluded that minimally invasive surgery is safe compared to medical therapy. But the primary outcome result of the trial is neutral. There was a small benefit with reduced mortality, but no significant benefit regarding functional outcome. Investigators suggest that this procedure might be beneficial if replicable in other studies. ■

Extending the Time for Thrombolysis to 9 Hours for Acute Ischemic Stroke (LB21)

SOURCE: Ma H, Campbell B, Churilov L, et al. Extending the thrombolytic time window to 9 hours for acute ischemic stroke using perfusion imaging selection: The final result. ISC 2019.

Intravenous thrombolysis for acute ischemic stroke currently is restricted to 4.5 hours from onset of symptoms, although viable brain tissue is present beyond that time.

Ma and colleagues from Australia conducted a multicenter, randomized, double-blind, placebo-controlled trial of alteplase in ischemic stroke patients presenting within 4.5 to 9 hours from onset of symptoms or in patients who had a wake-up stroke. Selection of patients for treatment was based on an automated perfusion imaging software (RAPID) that revealed salvageable brain tissue. Primary outcome was excellent functional outcome as measured by a modified Rankin scale (mRS) score of 0-1 at three months. Other outcomes included independent functional outcome, early reperfusion, improvement of the NIH stroke scale, death, and symptomatic intracerebral hemorrhage (ICH).

After 225 patients were randomized, the study was terminated because of early loss of clinical equipoise. The intention-to-treat analysis showed that patients who received alteplase achieved better functional outcomes: for mRS score 0-1, 35% vs. 29%, with an adjusted risk ratio of 1.44 ($P = 0.042$) and for mRS score 0-2, 50% vs. 43%, risk ratio = 1.36 ($P = 0.017$) at three months, with increased early reperfusion and clinical improvement based on reduction of the NIH stroke scale at 24 hours. Mortality was similar in both groups (12% vs. 9%), while symptomatic ICH was higher in the thrombolysis group (6% vs. 1%), as would be expected.

The investigators concluded that patients presenting within nine hours or with a wake-up stroke, selected by perfusion imaging, can achieve a significantly higher rate of excellent functional outcome compared to patients treated with placebo. The increase in rate of ICH is consistent with other thrombolytic trials, but this was not associated with increased mortality and it did not negate the beneficial effects and improved rate of excellent functional outcome in patients treated with thrombolysis. ■

Nitroglycerin for Prehospital Treatment of Acute Ischemic Stroke (LB2)

SOURCE: Bath PM, Scutt P, Woodhouse LJ, et al. Glyceryl trinitrate for prehospital ultra-acute stroke: Main results from the Rapid Intervention with Glyceryl Trinitrate in Hypertensive Stroke Trial 2 (RIGHT-2). Concurrently published in *Lancet* 2019; Feb. 6.

Glycerol trinitrate, known as nitroglycerin in the United States, is a nitric oxide that lowers blood pressure and has been shown in previous small trials to improve functional outcome and reduced death in patients with ischemic stroke and intracerebral hemorrhage (ICH) when given within six hours. Bath and colleagues from the United Kingdom tested whether nitroglycerin is safe and effective in improving outcome when administered by paramedics before hospital admission.

This was an ambulance-based, multicenter prospective, randomized, outcomes-blinded trial of patients with presumed stroke, either ischemic stroke or hemorrhagic stroke, and a systolic blood pressure of 120 mmHg or higher. Patients were randomized to nitroglycerin patch or sham patch within four hours of symptom onset. Treatment was initiated by paramedics on an ambulance. The primary outcome was a shift in the modified Rankin

scale (mRS) at three months. A total of 1,148 patients were enrolled by 516 paramedics from eight ambulance services from 2015 through 2018. Mean age was 73 years, 52% of patients were male, 57% had prior hypertension, 24% had prior stroke, 20% had diabetes, and 21% had atrial fibrillation. Mean blood pressure was 162/92 mmHg. Final diagnoses of the patients included ischemic stroke (51%), ICH (13%), transient ischemic attack (TIA; 9%), and stroke mimic (25%).

In patients treated with nitroglycerin, systolic blood pressure was lowered by 5.8 mm compared with the sham group. There was no difference in mRS score between the groups in participants with a final diagnosis of stroke or TIA. There were no significant differences in any of the mRS score groups. There were no differences in secondary outcomes, death, or serious adverse events between treatment groups. The investigators concluded that prehospital treatment with transdermal nitroglycerin does not seem to improve functional outcome in patients with presumed stroke. ■

Intensive Treatment of Hyperglycemia in Patients With Acute Stroke (LB1)

SOURCE: Johnston KC, Bruno A, Barrett KM, et al. Stroke Hyperglycemia Insulin Network Effort (SHINE) trial primary results.

Hyperglycemia is common in patients with acute stroke. Preclinical and clinical data show that hyperglycemia during acute cerebral ischemia is associated with worse outcome. At the same time, severe hypoglycemia increases injury to ischemic brain. In clinical studies, it is unclear if lowering glucose improves outcome. This study was designed to determine if intensive lowering of glucose with intravenous insulin will improve outcome in patients with acute ischemic stroke.

Johnston and colleagues from the University of Virginia randomized 1,151 patients enrolled at 63 sites across the United States between 2012 and 2018. Patients were randomized to treatment with intravenous insulin, targeting a blood sugar of 80-130 mg/dL vs. a standard subcutaneous sliding scale insulin treatment, with a target of 80-179 mg/dL. The primary outcome measure was 90-day modified Rankin scale (mRS), and the primary safety outcome was severe hypoglycemia, defined as < 40 mg/dL. Secondary outcomes included the 90-day NIH stroke scale, Barthel Index, and stroke-specific quality of life scale.

This study was stopped after 82% of patients had been enrolled after the fourth interim analysis determined futility. No safety Ballenger was crossed. There was no difference between the two groups in the primary efficacy outcome of mRS score. Although more incidents of severe hypoglycemia occurred in the intensive treatment group (2.6% vs. 0%), the episodes of hypoglycemia did not result in any negative or adverse outcomes. The investigators concluded that intensive glucose control does not improve 90-day functional outcome and increases the risk of severe hypoglycemia. Subcutaneous insulin with a target of < 180 mg/dL is the preferred treatment target. ■

ABSTRACT & COMMENTARY

Treatment of Acute Migraine With Ginger

By Louise M. Klebanoff, MD

Assistant Professor of Clinical Neurology, Weill Cornell Medical College

Dr. Klebanoff reports no financial relationships relevant to this field of study.

SYNOPSIS: Ginger extract has a long anecdotal history as a treatment for migraine headaches in traditional Chinese medicine. This well-designed study provides evidence that adding ginger to a standard nonsteroidal anti-inflammatory medication improves outcomes of migraine treatment by all measured parameters.

SOURCE: Martins LB, Rodrigues AMDS, Rodrigues DF, et al. Double-blind placebo-controlled randomized clinical trial of ginger (*Zingiber officinale* Rosc.) addition in migraine acute treatment. *Cephalgia* 2018; doi: 10.1177/0333102418776016. [Epub ahead of print].

Migraine is a common disabling primary headache disorder, affecting 12% of the population of the Western world. Although many medications are available for both the acute treatment and prevention of migraine, side effects and incomplete treatment relief lead to low satisfaction with current therapies. Increasingly, patients are turning to integrative treatment approaches, including nutraceuticals. Ginger (*Zingiber officinale* Rosc.) is a medicinal plant used for treating multiple conditions in China and India. The ginger rhizome contains several bioactive compounds. Volatile compounds are responsible for its aroma and flavor, and nonvolatile compounds, including gingerols and shogaols, are present in ginger extracts. The pharmacological activity of the nonvolatile compounds includes significant antiemetic, anti-inflammatory, antithrombotic, and analgesic effects, all of which could be helpful in the treatment of acute migraine. Several mechanisms have been proposed to explain the analgesic actions of ginger, including the inhibition of arachnoid acid metabolism via the

cyclooxygenase (COX) pathways and blocking lipoxygenase (LOX). In addition, shogaols may modulate the neuroinflammatory response through the down-regulation of inflammatory markers on microglial cells, and gingerols may act as agonists of the capsaicin-activated vanilloid receptors.

Martins et al performed a double-blind, placebo-controlled, randomized clinical trial with 60 participants comparing ginger to standard medical treatment in acute migraine. Patients experiencing a migraine attack of moderate or severe pain intensity were recruited through the emergency department of the Vera Cruz Hospital in Belo Horizonte, Brazil. Patients were between 18 and 60 years of age, had a diagnosis of migraine with or without aura for at least one year, and had one to six migraine attacks a month. The investigators evaluated headache impact using the Headache Impact Test version 6 (HIT-6) and the Migraine Disability Test (MIDAS). All patients with a migraine attack of moderate or severe intensity received ketoprofen 100 mg intravenously. Patients were randomized to receive 400 mg ginger extract or placebo. The primary endpoint was the proportion of patients who responded to treatment two hours after drug intake. Multiple secondary endpoints also were assessed.

Patients who received ginger reported lower pain intensity at one and two hours after drug intake. The proportion of patients who were pain free after two hours was higher in patients receiving ginger (56.7 vs. 33.3; $P = 0.03$) and more patients reported "no disability." Photophobia was reported less frequently in patients who took ginger. In both groups, no patient had vomiting after treatment. Most patients (73.1%) who received ginger extract reported being fully satisfied with treatment vs. 28.1% of patients receiving placebo ($P < 0.01$). Rescue medications were used by 13.3% of patients who received placebo compared to 8.7% of patients who received ginger. Side effects were not different between groups.

■ COMMENTARY

This well-designed, albeit small, double-blind, placebo-controlled, randomized clinical study found that ginger extract provided improved treatment response when added to standard therapy with ketoprofen. Ginger extract was well-tolerated. Patients receiving ginger had improved pain scores, disability scores, and treatment satisfaction when compared with placebo. There is historical anecdotal support for using ginger in multiple medical conditions, as well as experimental evidence of the mechanism of action of ginger as an anti-inflammatory and analgesic. Considering the frequency of migraine in the general population, the dissatisfaction with current treatment options, and the potential benefits of ginger extract with minimal side effects, ginger extract needs additional evaluation as both an acute and preventive treatment option for migraine. ■

ABSTRACT & COMMENTARY

Miller Fisher Syndrome: Atypical Features

By Michael Rubin, MD

Professor of Clinical Neurology, Weill Cornell Medical College

Dr. Rubin reports he is a consultant for Merck Sharp & Dohme Corp.

SYNOPSIS: Other than the classic triad of neurological signs that define Miller Fisher syndrome, it also is common to see delayed facial palsy, loss of taste, and weakness of pharyngeal and cervical muscles.

SOURCE: Jung JH, Oh EH, Shin JH, et al. Atypical clinical manifestations of Miller Fisher syndrome. *Neurol Sci* 2019;40:67-73.

Ophthalmoplegia, ataxia, and areflexia comprise the classic triad of Miller Fisher syndrome (MFS), a rare variant of Guillain-Barré syndrome (GBS), with an annual incidence of less than one patient per million population, and accounting for 5% of adults and 1.6% of children with GBS. About one-quarter demonstrate limb weakness, and some develop fixed dilated pupils. GQ1b antibodies are found in 90%, and nerve conduction studies show reduced or absent sensory responses with normal velocities. What is the spectrum and frequency of atypical features that may occur in MFS that are important to recognize, since they may lead to delayed or misdiagnosis?

Between 2012 and 2017, 38 patients with the classic MFS triad (pure MFS) were recruited consecutively from Pusan National University Yangsan Hospital in Gyeongsangnam-do, South Korea. Those with only two classic features were termed incomplete MFS, and those with additional features were termed overlapping MFS. Investigators reviewed all records, including demographics, neurological examination, pattern of clinical evolution, laboratory investigations, treatment, and outcome.
All 38 patients demonstrated the clinical triad at initial presentation, of which 68% (n = 26) remained pure MFS while 32% (n = 12) had an overlapping syndrome, encompassing MFS plus the pharyngeal-cervical-brachial

(PCB) variant of GBS in six, MFS plus GBS in four, and MFS plus Bickerstaff brainstem encephalitis (BBE) in two. Antecedent illness occurred in 89% (n = 34) prior to developing MFS, 68% (n = 26) were positive for anti-GQ1b antibodies, and five patients had additional anti-ganglioside antibodies, one each with anti-GM1 or anti-GM1/GD1b, and three with anti-GD1b.

Prior to initiation of intravenous immunoglobulin (IVIG) therapy, headache of moderate severity was present in 16% (n = 6) and tended not to respond to nonsteroidal anti-inflammatory agents, but resolved within two weeks. Delayed facial palsy developed in 8% (n = 3) within 10-16 days after disease onset, was unilateral in two and bilateral in one, and resolved fully in all three patients within two months. Only one patient with facial palsy had positive GQ1b antibodies. Divergence insufficiency without external ophthalmoplegia was seen in two, with esotropia at a distance. Within two months, these resolved with IVIG. Taste was lost over the entire tongue in two patients without facial weakness, but resolved within a month prior to ophthalmoplegia resolution. Overall, 30% of MFS patients have additional atypical features, awareness of which will avoid misdiagnosis and unnecessary investigations.

■ COMMENTARY

Acute ophthalmoparesis is the most common diagnosis among Korean children with anti-GQ1b antibody syndrome. In a retrospective study of 11 children, ages 5.4 to 18 years, with anti-GQ1b antibody syndrome, acute ophthalmoparesis occurred in six, classic MFS in two, and one each experienced acute ataxic neuropathy, MFS/GBS, or pharyngeal-cervical-brachial weakness. Variability of the clinical manifestations of anti-GQ1b antibody syndrome in children and adults is unclear, but may be related to differences in the specificity of anti-GQ1b antibodies and the different expression of gangliosides in the nervous system. Alternatively, variable accessibility of these antibodies to different parts of the nervous system also may result in varied clinical phenotype. Maturational change in GQ1b antigen expression and accessibility of anti-GQ1b antibodies are areas remaining to be explored.[1] ■

REFERENCE

1. Yoon L, Kim BR, Kim HY, et al. Clinical characterization of anti-GQ1b antibody syndrome in Korean children. *J Neuroimmunol* 2019; Jan 8. pii: S0165-5728(19)30008-6. doi: 10.1016/j.jneuroim.2019.01.003. [Epub ahead of print].

ABSTRACT & COMMENTARY

Precise Localization of Focused Ultrasound Thalamotomy Determines Clinical Benefit

By Harini Sarva, MD

Assistant Professor of Clinical Neurology, Weill Cornell Medical College

Dr. Sarva reports no financial relationships relevant to this field of study.

SYNOPSIS: Lesioning of the posterior portion of the VIM thalamus is most efficacious. Lesions extending beyond this portion can lead to adverse side effects in those with essential tremor treated with MRI-guided focused ultrasound.

SOURCE: Boutet A, Ranjan M, Zhong J, et al. Focused ultrasound thalamotomy location determines clinical benefits in patients with essential tremor. *Brain* 2018;141:3405-3414.

Boutet et al studied 66 of 91 patients who received MRI-guided focused ultrasound thalamotomy (MRgFUS) for medically refractory essential tremor. Subjects were excluded if they received a sham procedure as part of a clinical trial, did not have essential tremor, or had treatment targets other than the thalamus. Post-procedure assessments were performed at one day, one week, one month, and three months after treatment. The investigators used the Clinical Rating Scale for Tremor (CRST) to compare the tremor in the treated arm at baseline and at three months. The most common side effects noted from both subjective report and physical examination were sensory symptoms, dysarthria, ataxia, and motor symptoms (clumsiness or weakness). Lesion mapping was performed and accounted for the percent improvement on CRST. Thalamotomy lesion maps of patients with and without adverse events were drawn to determine the extent of thalamic involvement.

Using diffusion-weighted imaging and tractography, the investigators determined that the area that bordered between the VIM and VC regions of the posterior portion of the thalamus produced the best tremor response. This area was significantly different from the regions that produced adverse effects. When comparing the lesion maps, those that included the lateral thalamus were more likely to produce motor side effects, whereas those in the inferolateral region were more likely to produce ataxic symptoms including abnormal gait. When the thalamic somatosensory relay nuclei were affected there was a 38-times higher likelihood of acute sensory side effects in the immediate period after the lesioning.

Tractography confirmed that most of the lesions that resulted in a side effect overlapped the adjacent white matter tracts. Lesion volume > 170 mm^3 had a higher risk of producing acute post-procedure adverse effects.

■ COMMENTARY

MRgFUS lesioning provides patients with medically refractory essential tremor a minimally invasive therapy as an alternative to deep brain stimulation. The lack of drilling and cutting makes the MRgFUS appealing to patients who do not want implantable hardware. FUS has been shown to reduce tremor by approximately 40% in studies that compared baseline CRST with three-month CRST after the procedure. Long-term studies have shown that the positive lesioning effects are maintained for at least two years. However, unlike DBS, MRgFUS is not reversible and does not have intraoperative electrophysiological recording to improve lesion accuracy. Even slight spread of the lesion can lead to unwanted side effects. This study allows for better localization of the optimal site for tremor control. Further study using DWI, DTI, and perhaps even PET studies can assist in better accurately mapping the targets precisely to reduce unwanted lesioning-related side effects. In addition, long-term studies of the lesions and any adverse events that persist past three months need to be performed to reduce not only immediate postoperative side effects but also potentially permanent negative effects. Longer-term studies also will allow us to understand how patients recover from any side effects. ■

CME QUESTIONS

1. **There is no effective treatment for severe bleeding that occurs while taking Factor Xa inhibitor oral anticoagulants.**
   a. True
   b. False
2. **Dual antiplatelet treatment for acute ischemic stroke, combining cilostazol with aspirin, carries a high risk of long-term hemorrhagic complications.**
   a. True
   b. False
3. **The use of the iron chelating agent deferoxamine to treat intracerebral hemorrhage does not confer significant benefits.**
   a. True
   b. False
4. **Blood pressure management for patients with acute ischemic stroke should follow current guidelines to keep the systolic blood pressure below 180 mmHg.**
   a. True
   b. False
5. **Surgical evacuation of intracerebral hemorrhage has never been shown to improve outcome compared to best medical therapy.**
   a. True
   b. False
6. **In patients with acute ischemic stroke, administering intravenous thrombolytics beyond 4.5 hours does not result in any benefit and adds significant risk.**
   a. True
   b. False
7. **Current guidelines for treatment of hyperglycemia in patients with stroke should be followed to maintain blood sugar below 180 mg/dL.**
   a. True
   b. False
8. **When given in addition to ketoprofen, ginger extract was found to improve which of the following acute migraine-associated symptoms?**
   a. Overall disability
   b. Migraine aura
   c. Pain intensity at four hours
   d. Pain intensity at six hours

[IN FUTURE ISSUES]

Update on Multiple Sclerosis