NEUROLOGY ALERT®

Providing Evidence-based Clinical Information for 32 Years

A monthly survey of developments in neurologic medicine

AHC Media LLC Home Page—www.ahcmedia.com

CME for Physicians—www.cmeweb.com

AHC Media

INSIDE

Financial Disclosure: *Neurology Alert's* editor in chief, Matthew Fink, MD, is a retained consultant for Procter & Gamble. Peer reviewer M. Flint Beal, MD; executive editor Leslie Coplin; and managing editor Neill Kimball report no financial relationships relevant to this field of study.

Levodopa-Carbidopa Intraintestinal Infusion: Benefits in Advanced Parkinson's Disease

ABSTRACT & COMMENTARY

By Claire Henchcliffe, MD

Associate Professor of Neurology and Neuroscience, Weill Cornell Medical College

Dr. Henchcliffe reports she is on the speakers bureau and advisory board for GE, Teva Pharmaceutical Industries, and UCB; advisory board for Allergan and USWorldmeds; receives grant/research support from Biogen and Kaneka; and does CME program development and presentation for MedIQ.

Synopsis: *In this 12-week, randomized, double-blind and double-dummy trial, intrajejunal infusion of levodopa-carbidopa gel decreased "off" time by almost 2 hours more than oral levodopa-carbidopa in individuals with Parkinson's disease suffering motor fluctuations.*

Source: Olanow CW, et al. Continuous intrajejunal infusion of levodopa-carbidopa intestinal gel for patients with advanced Parkinson's disease: A randomized, controlled, double-blind, double-dummy study. *Lancet Neurol* 2014;13:141-149.

THIS 12-WEEK MULTICENTER, DOUBLE-BLIND, DOUBLE-DUMMY CLINICAL TRIAL assessed efficacy and safety of direct intrajejunal delivery of levodopa-carbidopa intestinal gel (LCIG) in advanced Parkinson's disease (PD). The primary outcome was change in daily motor "off" time measured by home diaries, i.e., time when PD symptoms were not controlled by medications. Seventy-one individuals with PD and levodopa-associated

Pharmacology Watch, *Clinical Briefs* Available Online

The March 2014 issues of *Pharmacology Watch* and *Clinical Briefs in Primary Care* are now available exclusively by e-mail or online. You can access these two valuable supplements to *Neurology Alert* at http://www.ahcmedia.com/supplements/. We will send PDF copies of these supplements to you by e-mail if you prefer. Please send an e-mail with your name and/or subscriber number to customerservice@ahcmedia.com with Digital AHC Supplements in the subject line. We welcome your feedback and appreciate your continued support as a subscriber to *Neurology Alert*.

VOLUME 32 • NUMBER 7 • MARCH 2014 • PAGES 49-56

NOW AVAILABLE ONLINE
www.ahcmedia.com

motor complications underwent placement of a percutaneous gastrojejunostomy tube attached to a pump and a cassette containing either LCIG or placebo gel. They were then randomized to receive either: 1) immediate-release oral levodopa-carbidopa (LC) plus placebo intestinal gel (n = 34), or 2) LCIG plus oral placebo tablets (n = 37). Participants in the two groups were well matched for age (63.7 ± 9.5 vs 65.1 ± 6.8 years for LCIG vs oral LC), PD disease duration (10.0 ± 4.6 and 11.8 ± 5.6 years for LCIG vs oral LC), and "off" time (6.3 ± 1.7 and 7.0 ± 2.1 hours daily for LCIG vs oral LC). "On" time with troublesome dyskinesias was approximately 1 hour in each group. Baseline daily levodopa doses were 1005 ± 374 mg (LCIG) and 1124 ± 478 mg (oral LC), and dopamine agonists, catechol-O-methyl transferase inhibitors, and monoamine oxidase B inhibitors were allowed. Subjects were started at their regular levodopa dose but were converted to immediate-release tablets containing 25 mg carbidopa and 100 mg levodopa. In those receiving LCIG, a morning bolus of 5-10 cc gel was followed by continuous infusion through waking hours and was stopped overnight. Investigators were allowed to adjust doses over the first 4 weeks. The study successfully met its primary outcome by reducing daily "off" time by -4.04 ± 0.65 hours (LCIG) vs -2.14 ± 0.66 hours (oral LC) (P = 0.0015). In parallel, "on" time without troublesome dyskinesias increased by 4.11 ± 0.75 hours (LCIG), and 2.24 ± 0.76 hours (oral LC) (P = 0.0059). "On" time without dyskinesias increased by 3.37 ± 1.04 hours (LCIG) vs 1.09 ± 1.05 hours (oral LC) (P = 0.0142). Serious adverse events occurred in 5/37 receiving LCIG and in 7/34 receiving oral LC. Many were related to the surgical procedure and device complications, but were mostly mild-to-moderate. Procedural pain was reported in 32%, wound infection in 17%, and post-procedural discharge in 10%. Intestinal tube malfunction included dislocation (24%) and occlusion (13%), and the tube was unintentionally removed in one subject. Pump malfunction occurred in 8%. Three subjects discontinued due to peritonitis and pneumonia (n = 1), psychosis (n = 1, LCIG group), or post-procedural discharge (n = 1), and two patients discontinued due to surgical complications.

■ COMMENTARY

Oral levodopa-carbidopa has been the "gold standard" of pharmacologic treatment of PD, but treatment results in dose- and duration-related motor complications in the majority of patients. Motor complications typically comprise end-of-dose wearing off (loss of benefit prior to the next scheduled dose) and dyskinesias that are often associated with peak dose. As PD progresses, patients are increasingly affected by fluctuating plasma levels of levodopa (which has a half-life of only 60-90 minutes) and erratic gastrointestinal absorption. Therefore, a need to "smooth out" levodopa delivery underpins the rationale for infusion technology tested in this trial. Results demonstrate clear superiority in reduction of "off" time for LCIG administration compared with oral LC. Although dopamine agonists, monoamine oxidase B inhibitors, and catechol-O-methyl transferase inhibitors decrease "off" time, a simultaneous increase in dyskinesia and other side effects limit benefit in some patients. In such situations, deep brain stimulation may be an option, but is not suitable for all patients and is associated with rare but potentially serious complications. The authors raise the intriguing point of whether smoother levodopa delivery will improve dyskinesias, but proving this will require a longer study. In the meantime, it is encouraging that plasma levodopa levels were less variable in those receiving LCIG vs oral LC. The majority of adverse events were related to either placement or function of the percutaneous gastrojejunostomy tube and pump, and patients and caregivers will need to be well counseled, educated, and trained when starting LCIG. Common levodopa-associated side effects, such as nausea, were also recorded in both groups. One group has previously reported polyneuropathy and Guillain-Barré syndrome in association of LCIG use, but no such instances were found in this study. In summary, this is the first double-blind study to demonstrate LCIG superiority over oral LC in PD. LCIG is currently in use for PD with motor complications in more than 40 countries, so there is ample experience to further support its use. If and when LCIG reaches the market in the United States, it should provide an important new treatment in selected patients struggling to manage fluctuating symptoms of advanced PD. ■

Neurology Alert, ISSN 0741-4234, is published monthly by AHC Media LLC, One Atlanta Plaza, 950 East Paces Ferry Road NE, Suite 2850, Atlanta, GA 30326.

EXECUTIVE EDITOR: Leslie G. Coplin
MANAGING EDITOR: Neill L. Kimball
EDITORIAL DIRECTOR: Lee Landenberger

GST Registration Number: R128870672.

Periodicals Postage Paid at Atlanta, GA 30304 and at additional mailing offices.

POSTMASTER: Send address changes to *Neurology Alert,* P.O. Box 550669, Atlanta, GA 30355.

Back Issues: $42. Missing issues will be fulfilled by customer service free of charge when contacted within one month of the missing issue's date.

Subscriber Information

Customer Service: 1-800-688-2421.
Customer Service E-Mail: customerservice@ahcmedia.com
Editorial E-Mail: leslie.coplin@ahcmedia.com
Online: www.ahcmedia.com

Subscription Prices

United States
1 year with free AMA Category 1 credits: $369
Add $19.99 for shipping & handling.
(Student/Resident rate: $125)
Online only, single user: $319
Multiple Copies
Discounts are available for group subscriptions, multiple copies, site-licenses or electronic distribution. For pricing information, call Tria Kreutzer at 404-262-5482.
Canada
Add 7% GST and $30 shipping.
Elsewhere
Add $30 shipping.

Accreditation

AHC Media is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

AHC Media designates this enduring material for a maximum of *25 AMA PRA Category 1 Credits™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

This CME activity is intended for the neurologist. It is in effect for 36 months from the date of the publication.

AHC Media

Questions & Comments
Please contact **Leslie Coplin**, Executive Editor, at leslie.coplin@ahcmedia.com.

Can Measuring Iron in MS Provide Insight into Disease?

ABSTRACT & COMMENTARY

By Susan Gauthier, DO, MS

Assistant Professor of Neurology, Weill Cornell Medical College

Dr. Gauthier reports she receives research support from EMD Serono, Biogen Idec, and Novartis Pharmaceuticals, and is on the speakers bureau for Biogen Idec and Teva Neurosciences.

Synopsis: *In a large histopathological study, the distribution of nonheme iron and the expression of iron-related proteins in multiple sclerosis (MS) brains were compared to controls. There was an age-related increase in iron found in control white matter but not within the normal appearing white matter of MS patients with longer disease durations.*

Source: Hametner S, et al. Iron and neurodegeneration in the multiple sclerosis brain. *Ann Neurol* 2013;74:848-861.

IRON, STORED WITHIN THE CENTRAL NERVOUS SYSTEM PRIMARily as non-heme iron within oligodendrocytes and myelin, has the potential to contribute to oxidative damage, and its role in many neurodegenerative diseases is being investigated. In multiple sclerosis (MS), imaging studies have revealed a higher deposition of iron within the basal ganglia of patients as compared to controls and suggested that lesions may have high levels of iron. Utilizing quantitative susceptibility mapping, our group found changes in MS lesion susceptibility (presumed to be predominantly due to iron) that was dependent on the age of the lesion.[1] In this study by Hemetner et al, the authors attempted to gain an improved understanding of the white matter iron dynamics occurring in MS.

Tissue from 33 MS brains and 30 control cases were analyzed for this study. Optical densitometry and cellular staining were used to measure the iron distribution within the brain samples. The patient population ranged from acute MS (clinical course leading to death within 1 year) to relapsing and progressive subtypes. Nonheme iron within the white matter of control cases had a strong correlation with age ($r = 0.899$, $P < 0.001$) whereas MS patients failed to show this association ($r = 0.087$, $P = 0.659$). Furthermore, there was a reduction in iron load in MS patients with increasing disease duration ($r = -0.558$, $P < 0.001$). Oligodendrocytes expressing membrane-bound, iron-exporting ferroxidases were decreased in MS normal-appearing white matter; however, they were increased closer to periplaque white matter. Among MS lesions, the highest iron load was appreciated at the edges of classic, active, slowly expanding, and some inactive plaques, but not present at the edges of remyelinated lesions. Across all lesions, 8% had more iron as compared to normal-appearing white matter, 27% contained a similar amount, and 65% contained less. In active lesions, demyelination and oligodendrocyte destruction were prominent within the periplaque white matter and decreased toward the lesion center. Active lesions were found to have iron-reactive granules in the extracellular space as well as within endosomes or lysosomes of microglia/macrophages. Toward the center of lesions, the number of iron-containing microglia/macrophages decreased and, if iron was present, it was seen most often within astrocytes, axons, and occasional macrophages. At the rim of inactive (or chronic) lesions, iron-containing microglia demonstrated dystrophic features indicating degeneration, and in contrast, these findings were rarely appreciated among remyelinated lesions. Lastly, axonal sphericals, indicating acute axonal injury linked to oxidative damage, were most abundant in actively demyelinating lesions.

■ COMMENTARY

As patients with MS age, the normal-appearing white matter lacks the normal accumulation of non-heme iron and may be due to a loss of myelin and/or oligodendrocytes or a loss of oligodendrocytes that specifically contain iron. The higher population of oligodendrocytes with an upregulation of iron-exporting ferroxidases near the lesion edge suggests that inflammatory mediators might facilitate iron export from these cells. Given that oligodendrocytes require iron for active myelination, these observed alterations in glial iron homeostasis may represent one mechanism contributing to remyelination failure in MS. The authors imply there are two sequential waves of iron liberation in MS lesions: 1) release of iron from damaged oligodendrocytes (and myelin loss) in active lesions and 2) release of iron from degenerating microglia/macrophages in chronic lesions. The iron is eventually removed from chronic lesions, yet the duration of extracellular iron exposure is unknown and important to consider given its potential to propagate a continued inflammatory process and promote oxidative damage within lesions.

This study demonstrates an alteration of the normal iron homeostasis within the white matter of MS patients. We have yet to fully understand the significance of these observed dynamics and/or how to approach from a therapeutic standpoint. However, it is reasonable to assume that iron may impact normal tissue repair or remyelination as well as further contribute to oxidative stress and mitochondrial dysfunction, all of which leads to neuronal loss in MS. ■

Reference

1. Chen W, et al. Quantitative susceptibility mapping of multiple sclerosis lesions at various ages. *Radiology* 2013; Nov 18. doi: http://dx.doi.org/10.1148/radiol.13130353.

Stroke Alert: A Review of Current Clinical Stroke Literature

By Matthew E. Fink, MD, *Professor and Chairman, Department of Neurology, Weill Cornell Medical College, and Neurologist-in-Chief, New York Presbyterian Hospital*

Thromboembolic Complications of Pregnancy, Including Stroke, May Persist For Up to 12 Weeks Postpartum

Source: Kamel H, et al. Risk of a thrombotic event after the 6-week postpartum period. *N Engl J Med* 2014; Feb 13. Online DOI: 10.1056/NEJMoa1311485.

THE POSTPARTUM STATE IN HEALTHY WOMEN IS ASSOCIATED with a variety of thromboembolic complications, including ischemic stroke. During pregnancy, all of the intrinsic clotting factors increase to a maximum around the time of delivery, and then gradually decline to normal by about 6 weeks postpartum. Based on that information, it was believed that the risk of thromboembolism would persist up to 6 weeks postpartum. But little epidemiological evidence existed to confirm or dispute this hypothesis.

Kamel et al used a claims database on all discharges from nonfederal emergency departments and acute care hospitals in California, and identified women who were hospitalized for labor and delivery between January 1, 2005, and June 30, 2010. In addition, they tabulated a composite primary outcome of ischemic stroke, acute myocardial infarction, or venous thromboembolism in those same women. They then used logistic regression to assess each patient's likelihood of a first thrombotic event during sequential 6-week periods after delivery, as compared with the corresponding 6-week period 1 year later.

Among the 1,687,930 women with a delivery, 1015 had a thrombotic event (248 cases of stroke, 47 cases of myocardial infarction, and 720 cases of venous thromboembolism) in the period of 1 year plus up to 24 weeks after delivery. The risk of primary thrombotic events was markedly higher within 6 weeks after delivery than in the same period 1 year later, with 411

A New, Effective Treatment for Obstructive Sleep Apnea: Hypoglossal Nerve Stimulation

ABSTRACT & COMMENTARY

By Alan Z. Segal, MD

Associate Professor of Clinical Neurology, Weill Cornell Medical College

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

Synopsis: *Tongue protrusion, via hypoglossal nerve stimulation, appears to have great efficacy in the treatment of obstructive sleep apnea in this uncontrolled, large case series.*

Source: Strollo PJ Jr, et al. Upper-airway stimulation for obstructive sleep apnea. *N Engl J Med* 2014;370:139-149.

OBSTRUCTIVE SLEEP APNEA (OSA) IS A KNOWN RISK FACTOR for stroke, myocardial infarction, and overall mortality. Continuous positive airway pressure (CPAP) continues to be the mainstay therapy for this disorder, but is plagued by adherence rates as low as 30%. CPAP is better tolerated with optimization of mask fitting, strategies such as daytime adaptation, and close follow-up and monitoring. Even with these maneuvers, however, a large proportion of patients cannot tolerate CPAP. There are alternative therapies to CPAP, including oral appliances to advance the mandible and surgeries such as uvulopalatopharyngoplasty (UPPP), but these are of modest benefit, particularly in cases of moderate-to-severe OSA. Due to these limitations and the overall prevalence and dangers of OSA, the potential benefits for upper airway (tongue) stimulation shown here are particularly exciting.

In OSA, there is excessive relaxation of pharyngeal musculature leading to airway collapse. The genioglossus muscle, responsible for tongue protrusion, is a major contributor to this loss of airway patency as the base of the tongue falls backwards into the airway. This phenomenon is frequently observed in patients with "positional apnea," who snore or obstruct when on their back but improve when turned sideways. In these patients, genioglossus function may be sufficient to push the tongue out of the airway when positioned laterally, but too weak to do so when supine. Devices designed to pull the tongue forward are uncomfortable and ineffective. Hypoglossal nerve stimulation is a more effective strategy, facilitating gengioglossus activity and tongue protrusion. This device includes an excitatory electrode placed unilaterally on the hypoglossal

events vs 38 events, for an absolute risk difference of 22.1 events (95% confidence interval [CI], 19.6-24.6) per 100,000 deliveries and an odds ratio of 10.8 (95% CI, 7.8-15.1). There was also a significant increase in risk during the period of 7 to 12 weeks after delivery as compared with the same period 1 year later, with 95 vs 44 events, for an absolute risk difference of 3.0 events (95% CI, 1.6-4.5) per 100,000 deliveries and an odds ratio of 2.2 (95% CI, 1.5-3.1). Risks of thrombotic events were not significantly increased beyond the first 12 weeks after delivery. Further prospective study is indicated to identify the mechanisms of these complications and develop preventive strategies. ■

Stroke After an Episode of Transient Global Amnesia Is Rare

Source: Mangla A, et al. Transient global amnesia and the risk of stroke. *Stroke* 2014;45:389-393.

Transient global amnesia (TGA) is a common disorder that often generates great anxiety in both patient and physician because of its similarity to the symptoms of ischemic stroke. The mechanism of TGA has been hotly debated and attributed to transient ischemia, migraine, and epileptic seizure, but the cause and pathophysiology have never been definitively proven.

The authors searched a California hospital claims database to determine the risk of stroke following an episode of TGA, and compared this to the risk of stroke following migraine, transient ischemic attack (TIA), and an epileptic seizure. After an episode of TGA, the cumulative 1-year rate of stroke was 0.54% (95% confidence interval [CI], 0.36-0.81), after migraine was 0.22% (95% CI, 0.20-0.25), after seizure was 0.90% (95% CI, 0.83-0.97), and after TIA was 4.72% (95% CI, 4.60-4.85). After adjustment for demographic characteristics and stroke risk factors, TGA was not associated with stroke risk when compared with migraine (HR, 0.82). The risk of stroke after TGA was lower than after an epileptic seizure (hazard ratio [HR], 0.57) or after a TIA (HR, 0.27). The natural history of TGA suggests a migrainous mechanism and stroke risk that is similar to that following a migraine. ■

nerve and a sensing electrode in the chest, which monitors intercostal muscle activity and allows stimulation timed to the inspiratory phase of ventilation.

The present multicenter study included 126 patients with a history of OSA who were non-adherent to CPAP therapy. More than 900 patients were screened for the study using the apnea-hypopnea index (AHI), with the majority of exclusions due to OSA that was too mild (AHI < 20; n = 324) or too severe (AHI > 50; n = 87). The AHI scores apneas (reductions in airflow > 90%) and hypopneas (reductions in airflow > 30% accompanied by a 4% drop in oxygen saturation) throughout the duration of sleep, with the total number of events converted into an hourly rate index. In addition to requiring an AHI range of 20-50, the study excluded patients with central or mixed obstructive-central events, as well as those with positional apnea (non-supine AHI < 10). Also excluded were patients with markedly enlarged tonsils or with total airway collapse on endoscopic examination. Additionally, patients with significant comorbidities or with a body mass index (BMI) > 32 kg/m^2 were excluded.

After 1 year of stimulator therapy, the AHI in study participants decreased from 29 to 9, a 68% reduction that was highly statistically significant ($P < 0.001$). The Oxygen Desaturation Index, defined as the number of times per hour that oxygen saturation dropped by more than 4%, decreased from 25 to 7, a 70% reduction that was also highly statistically significant. The time spent with O_2 saturations < 90% was also significantly reduced. Dramatic benefits were also seen on the Epworth Sleepiness Scale and the Functional Outcome of Sleep Questionnaire, confirming that the improvements in OSA were robust and directly improved daytime alertness and cognitive function. Of note, participants did not lose weight over the course of the study (which might have been an alternative explanation for their improvement), showing a mean BMI of 28 kg/m^2 at baseline and at 12 months. Following the 12-month study, a consecutive subset of patients who benefitted from the stimulator (n = 46) were randomized to an additional week with or without the device turned on. In the withdrawal group, the AHI increased from 7 to 26 in one week, compared to essentially no change in the patients continued on stimulator therapy. Serious adverse events (n = 2) requiring lead repositioning due to discomfort were rare. Nine patients required a tooth guard due to tongue abrasion.

■ COMMENTARY

This study represents a possible paradigm shift in the management of OSA, providing convincing evidence of the efficacy of stimulator therapy. There do remain limitations in its overall conclusions. The investigators chose patients in the "sweet spot" of OSA severity, AHI 20-50, having moderate-to-severe, but not very severe disease. Patients with milder OSA (AHI < 20) have significant

OSA-associated morbidity that cannot be ignored. Patients in the very severe category (AHI > 50), not included in this study, might not be helped by hypoglossal nerve stimulation but perhaps could be treated with lower CPAP pressures, which would promote adherence.

Patients with BMI > 32 kg/m^2 were excluded. This would include a subset of patients with mild-moderate obesity (BMI 30-35 kg/m^2) and eliminate anyone with severe (BMI 35-40 kg/m^2) or morbid (BMI > 45 kg/m^2) obesity. With increasing weight, excessive neck soft tissue in obese patients contributes to airway collapse even in the presence of optimal tongue positioning. It is not clear, however, if the cutoff point used in this study represents the upper limit of efficacy for this therapy.

The study used a "permissive" definition of a positive response to therapy, using criteria of AHI < 20 and overall AHI reduction by 50%, as evidence of benefit. Patients with AHI values in the 5-20 range are treated with CPAP by many practitioners. Furthermore, successful CPAP therapy is typically considered to be "curative" when AHI is reduced into the normal range (< 5). Even with the liberal definition of treatment effect used in this study, 34% of study subjects did not achieve benefit. Given the profound reductions in mean AHI, there may have been significant inter-subject variability in treatment response.

There is a significant cost differential between CPAP therapy ($1500 for a state-of-the-art machine) and hypoglossal nerve stimulation (approximately $30,000 for the device alone, excluding surgical costs). This may be cost efficient, however, given the major expenses associated with OSA-associated morbidity and mortality, especially in patients who would not otherwise use CPAP.

Hypoglossal nerve stimulation represents a potentially exciting advance in the management of OSA. If a randomized, controlled trial confirms its efficacy, it may become the mainstay of OSA treatment. ■

Demyelination and Deoxygenation?

ABSTRACT & COMMENTARY

By Joseph E. Safdieh, MD

Assistant Professor of Neurology, Weill Cornell Medical College

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

Synopsis: *In an animal model, hypoxia may play a significant role in causing tissue damage and neurologic deficits in demyelinating disorders, and early oxygen therapy may improve function.*

Source: Davies AL, et al. Neurological deficits caused by tissue hypoxia in neuroinflammatory disease. *Ann Neurol* 2013;74:815-825.

Multiple sclerosis is a neurologic disorder that causes multifocal episodes of central nervous system demyelination as well as delayed neurodegeneration with many possible neurologic symptoms and signs. However, various previous studies have concluded that inflammation alone may be sufficient to cause clinical deficits without demyelination. The authors of this study attempt to prove that tissue hypoxia plays a significant role in the development of neurologic deficits in an animal model of demyelination.

The authors induced experimental autoimmune encephalomyelitis (EAE) in rats by immunizing them with recombinant myelin oligodendrocyte glycoprotein. The rats developed typical EAE with an early asymptomatic phase, the first peak of symptoms, remission, and relapse. Control and experimental animals were studied. Animals were grouped by disease phase and were injected with pimonidazole 4 hours prior to terminal anesthesia. Pimonidazole readily enters CNS tissues and is converted to a form that permanently binds hypoxic tissue but does not bind to tissues with normal oxygenation. A cohort of the animals underwent in vivo oxygen probe measurement as well to detect spinal cord tissue oxygenation at various phases of EAE.

The authors looked at spinal cord tissue in EAE and control animals. Animals with EAE demonstrated severe inflammation of the spinal cord in association with the development of ascending weakness. Activated microglia were detected primarily in the white matter and meninges of the EAE animals, but also noted in the gray matter, and their presence correlated with the degree of neurologic deficit. Significant pimonidazole labeling was detected in the lumbar spinal cord of EAE animals, and the intensity of labeling correlated with severity of neurologic deficit, and returned to normal during remission. Pimonidazole labeling was present in both the gray matter and white matter of EAE animals, and was not detected in control animals. Of note, no demyelination was noted in the initial attack of EAE by luxol fast blue staining. From these results, the authors concluded that the inflamed tissue in EAE spinal cord, but not controls, was hypoxic, based on pimonidazole labeling.

To further study this phenomenon, the authors then performed in vivo spinal cord oxygen probe measurements in anesthetized animals in the EAE and control groups. They determined that controls had normal spinal cord oxygenation whereas EAE animals had significant spinal cord hypoxia, which normalized during remission and became hypoxic again during relapse. Additionally, spinal cord vessel size differed significantly between the EAE and control groups, with larger diameter vessels in the EAE

groups. This would be consistent with vascular compensation for tissue hypoxia. Vessel size was greatest during the relapse phase in EAE animals.

The authors then performed a study treating the animals with normobaric oxygen therapy (95% oxygen) vs room air acutely at onset of first neurologic deficit. These animals were also terminally anesthetized after pimonidazole injection. Notably, labeling for pimonidazole was absent in the oxygen-treated animals suggesting normal spinal cord oxygenation, and this was further demonstrated in vivo with spinal cord oxygen probe measurements. Another finding was that acute oxygen administration improved the expression of neurologic deficits in EAE animals compared to those administered room air. Continuous oxygen therapy for the next 7 days led to persistence of functional improvement.

■ COMMENTARY

This study is important for several reasons. First, it demonstrates that inflammatory changes in EAE are associated with tissue hypoxia in the absence of demyelination. Second, it demonstrates that acute oxygen therapy at the onset of deficits mitigates these tissue changes and leads to functional improvement. These findings are provocative and should lead to further study of the role of tissue hypoxia in multiple sclerosis. Perhaps a study of acute oxygen therapy in patients with relapses of multiple sclerosis might be undertaken based on these findings. That said, caution should be used before applying the results of animal studies of EAE to humans with multiple sclerosis without further clinical investigation in a placebo-controlled trial. ■

Thymectomy for Juvenile Myasthenia

ABSTRACT & COMMENTARY

By Michael Rubin, MD

Professor of Clinical Neurology, Weill Cornell Medical College

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

Synopsis: *Although never confirmed in a randomized clinical trial, thymectomy appears to be efficacious in children with antibody-positive myasthenia gravis.*

Source: Heng HS, et al. Outcome of children with acetylcholine receptor (AChR) antibody positive juvenile myasthenia gravis following thymectomy. *Neuromuscul Disord* 2014:24:25-30.

Despite the lack of randomized, controlled trials, thymectomy is widely accepted as a treatment option for both seropositive and seronegative generalized myasthenia gravis (MG), even in the absence of thymoma. Thymectomy, however, remains controversial for the 10-16% of patients whose onset occurs before 15 years of age, and this retrospective review addresses the issue.

Medical record review was undertaken of patients with juvenile MG who underwent thymectomy between January 1996 and June 2010, at two London, UK, hospitals, Evelina Children's Hospital and Great Ormond Street Hospital for Children. Of 21 patients so identified, 20 had generalized MG, had undergone trans-sternal thymectomy, and are the subjects of this report. Disease severity was graded using the modified Osserman classification, grade 1 (focal disease) to grade 4 (life-threatening crisis), and patients were seen 1 month postoperatively, and every 3 months thereafter for a year. Response was rated using the Millichap and Dodge myasthenia scale, with A denoting complete remission, B good improvement needing medication, C slight improvement needing increased dosage of medication, D no change or worse, and E death.

Disease onset ranged from 13 months to 15.5 years of age. Median interval from disease onset to thymectomy was 9 months, with a median age at thymectomy of 11 years 1 month, ranging from 2 years 8 months to 16 years. Five children were younger than 10 years, of which two were younger than 3 years. All were acetylcholine receptor (AchR) antibody positive, with no correlation found between antibody level and disease severity. Prior to surgery, treatment included pyridostigmine (n = 20), oral prednisolone (n = 14), elective plasma exchange (n = 15), or intravenous immunoglobulin (n = 5). Thymic hyperplasia was found in nine patients, normal histology in six patients, thymoma in one patient, and no report was available for the remainder. At last follow-up, ranging from 10 months to almost 11 years (median 2.66 years), 19 of 20 were improved, with six in complete remission (A response), 12 showing good improvement but needing medication (B response), and one each showing C and D response, the nonresponder being the patient with thymoma. Thymectomy is safe and efficacious for the treatment of AchR antibody positive juvenile myasthenia gravis.

■ COMMENTARY

Thymic resection may be done by a conventional transsternal approach or via video-assisted thoracoscopic surgery (VATS). How do they compare? Among 120 patients with early-stage thymoma, who underwent thymectomy between 1991-2010 at the National Taiwan University Hospital, Taipei, Taiwan, 76 underwent VATS and 44 conventional sternotomy.[1] Among the VATS group, 35 patients (46.1%) presented with myasthenia, compared to 14 (31.8%) in the sternotomy group. Neither group experi-

enced significant complications or surgical-related mortality. Both groups had similar overall survival, recurrence-free survival, and time to tumor recurrence, but the VATS group experienced a significantly shorter time for both chest tube pleural drainage and hospital stay. Duration of surgery, visual analog pain score, and intraoperative blood loss were not significantly different between the groups, though all were lower in the VATS patients. VATS appears to be as good as, if not preferable to, sternotomy for early-stage thymoma removal, and, likely, for thymectomy in myasthenia as well. ■

CME Objectives

Upon completion of this educational activity, participants should be able to:

- discuss current scientific data regarding the diagnosis and treatment of neurological disease;
- discuss the pathogenesis and treatment of pain;
- describe the basic science of brain function;
- discuss new information regarding new drugs for commonly diagnosed neurological conditions and new uses for traditional drugs;
- identify nonclinical issues of importance for the neurologist.

CME Instructions

To earn credit for this activity, follow these instructions:

1. Read and study the activity, using the provided references for further research.
2. Scan the QR code at the right or log on to www.cmecity.com to take a post-test; tests can be taken after each issue or collectively at the end of the semester. First-time users will have to register on the site using the 8-digit subscriber number printed on their mailing label, invoice or renewal notice.
3. Pass the online tests with a score of 100%; you will be allowed to answer the questions as many times as needed to achieve a score of 100%.
4. After successfully completing the last test of the semester, your browser will be automatically directed to the activity evaluation form, which you will submit online.
5. Once the completed evaluation is received, a credit letter will be e-mailed to you instantly.

Reference

1. Liu TJ, et al. Video-assisted thoracoscopic surgical thymectomy to treat early thymoma: A comparison with the conventional transsternal approach. *Ann Surg Oncol* 2014;21:322-328.

CME Questions

1. Intrajejunal infusion, via percutaneous gastrojejunostomy tube, of levodopa-carbidopa intestinal gel in Parkinson's disease patients with motor fluctuations has been shown to:
a. decrease "off" time.
b. decrease dyskinesias.
c. increase plasma levodopa concentration fluctuation.
d. provide a first line therapy for early PD.
e. avoid nausea as a side effect.

2. Hypoglossal nerve stimulation helps to correct obstructive sleep apnea by which of the following mechanisms?
a. It increases the rate of breathing.
b. It reduces airway obstruction by initiating tongue protrusion.
c. It has no effect on the apnea-hypopnea index.
d. It causes frequent awakenings and therefore stimulates breathing.

3. What is the initial wave of iron liberation in an acute lesion believed to represent?
a. Release from axons
b. Release from astrocytes
c. Release from iron-containing oligodendrocytes and myelin
d. Release from dystrophic microglia
e. All of the above

4. In an animal model of experimental autoimmune encephalomyelitis, early oxygen therapy improved functional outcomes.
a. True
b. False

5. Thymectomy for myasthenia gravis:
a. is not indicted for generalized, acetylcholine receptor antibody positive, juvenile myasthenia gravis.
b. is indicted for generalized, acetylcholine receptor antibody positive, juvenile myasthenia gravis.
c. should preferably be performed by sternotomy rather than by video-assisted thoracoscopic surgery.

6. A healthy pregnancy does not carry any additional risk of thromboembolic complications.
a. True
b. False

7. Transient global amnesia carries a high risk of subsequent ischemic stroke.
a. True
b. False

In Future Issues:

The Latest Alzheimer's Disease Clinical Trials