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 MAQUET. 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.

Efficacy of Continuous EEG Monitoring in Critical Care Units

ABSTRACT & COMMENTARY

By Elayna Rubens, MD

Assistant Professor of Neurology, Weill Cornell Medical College

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

Synopsis: *Utilization of continuous EEG monitoring in mechanically ventilated patients in the ICU was associated with a reduction in hospital mortality without significantly affecting hospital costs or length of stay.*

Source: Ney JP, et al. Continuous and routine EEG in intensive care. *Neurology* 2013;81:2002-2008.

As the technology for obtaining, storing, and reviewing digital EEG has expanded over the last 10 years, so has the utilization of continuous electrocencephalography monitoring (cEEG). In the ICU setting, cEEG has become an important tool in the diagnosis and management of non-convulsive seizures, status epilepticus, and other changes in cerebral function such as ischemia. With its increased utilization, controversy has emerged about the cost effectiveness of cEEG and its overall impact on patient outcome. In this study, Ney et al examined the effect of cEEG monitoring in critically ill patients on inpatient mortality, length of stay, and hospital charges.

AHC Media is Going Digital!

The February 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 6 • FEBRUARY 2014 • PAGES 41-48

NOW AVAILABLE ONLINE
www.ahcmedia.com

This is a retrospective, cross-sectional study conducted using data from the Nationwide Inpatient Sample (NIS), the largest all-payer inpatient database containing clinical and demographic information from approximately 20% of all discharges from non-federal U.S. hospitals. All patients who underwent mechanical ventilation and EEG (either cEEG or routine EEG) between 2005-2009 were included in the study. In-hospital mortality was the primary outcome measure, while length of stay and hospitalization charges were secondary outcomes. The group undergoing cEEG was compared to the group that had routine EEG alone for all outcome measures. Multivariate regression analysis included comorbidities, demographics, and hospital variables. In addition, separate subgroup analysis was performed on groups of patients with epilepsy/seizure diagnosis, neurologic diagnosis, or EEG performed on the day of discharge.

A total of 40,945 inpatient discharges were included in the analysis. Of these, 5949 underwent cEEG monitoring and 34,996 underwent routine EEG only. The group undergoing cEEG was significantly younger, less likely to have Medicare, and more likely to have a neurologic or epilepsy diagnosis. Hospitals performing cEEG were more likely to be larger, academic centers. The use of cEEG increased dramatically from 2005 to 2009 (by 263%). Inpatient mortality in ventilated patients receiving cEEG was significantly reduced when compared to patients undergoing routine EEG only (25% vs 39%; odds ratio [OR], 0.54) even when adjusting for demographics, hospital characteristics, and comorbidities (OR, 0.63; $P < 0.001$). Total hospital charges and length of stay tended to be increased in the cEEG group compared to the routine EEG group, but were not significantly different. Subgroup analysis of patients with neurologic/epilepsy diagnosis revealed that these diagnoses were more common in the cEEG group and were positively associated with survival. Routine EEG performed on the day of discharge was highly associated with mortality, since EEG is used to confirm brain death in some hospitals. When any of these subgroups was used as a covariate in the analysis, or excluded from the multivariate regression calculations, there was no change in the association between cEEG and inpatient mortality.

The authors concluded that cEEG monitoring in ICU patients is associated with improved patient survival compared to routine EEG alone. They propose that the survival benefit stems from the ability to detect and, therefore, treat brain dysfunction more accurately and responsively with cEEG monitoring. In addition, the study found no significant increase in hospitalization cost or length of stay in those patients undergoing cEEG monitoring. Together, these results support the use of cEEG monitoring in the ICU setting as a clinically valuable and potentially cost-effective tool.

■ COMMENTARY

Previous research on cEEG monitoring in critically ill patients has focused on the diagnostic value of cEEG monitoring and its role in modifying ICU management and clinical decision-making. Such research has demonstrated that the diagnostic effectiveness of cEEG monitoring in critically ill patients exceeds that of routine EEG. It is now well established that utilizing cEEG monitoring in the ICU leads to change in management in a significant number of patients. The current study is an important contribution to the cEEG literature, as it takes the impact of cEEG a step further: patient outcome. By demonstrating an association of cEEG with improved survival in a large cohort of patients, the authors are able to provide further justification for cEEG monitoring and its implicit resource utilization among critically ill patients.

The study's design as a retrospective study allowed the researchers to obtain a large enough sample size to test outcome-based hypotheses. The limitations of the design, however, are that the results cannot be used to infer causation. There may be a number of alternative explanations (differences between comparison groups, improvement in ICU care concurrent with cEEG utilization, etc.) for the association of cEEG with improved survival, only some of which can be adequately adjusted for in the data analysis. Further prospective studies of cEEG in critically ill patients are needed to confirm the survival benefits and cost effectiveness of cEEG monitoring. ■

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.

Prolonged Release Oxycodone-Naloxone for Treatment of Severe RLS

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: *This 12-week, randomized, double-blind, placebo-controlled trial examined the combination of oxycodone and naloxone for treatment of severe restless legs syndrome in patients inadequately controlled by previous treatment. An open-label, 40-week extension study supported long-term efficacy of this treatment.*

Source: Trenkwalder C, et al. Prolonged release oxycodone-naloxone for treatment of severe restless legs syndrome after failure of previous treatment: A double-blind, randomized, placebo-controlled trial with an open-label extension. *Lancet Neurol* 2013;12:1141-1150.

This 12-week, multicenter, European clinical trial used a randomized, double-blind, placebo-controlled design to assess efficacy of prolonged-release oxycodone-naloxone for treatment of patients with severe restless legs syndrome (RLS). Individuals with secondary causes of RLS and those with serum ferritin < 30 pg/mL were excluded. All subjects had onset of symptoms before 1800 h at least 4 days a week. Previous treatment failure, mostly with dopamine agonists or levodopa, was due to either lack of efficacy or intolerable side effects. All previous treatments were tapered off prior to the start of the trial, so that at randomization, subjects had not received any RLS treatment for 7 days. In the treatment and placebo arms of the study at baseline, mean age was 63.1 ± 11.4 years and 61.7 ± 11.0 years, respectively; symptom duration was approximately 10 years in each group; and the International RLS (IRLS) Study Group rating scale score was approximately 28 in each group, denoting severe symptoms (scale range is 0-40). In the treatment arm, the starting dose was oxycodone 5 mg plus naloxone 2.5 mg twice daily, which could be titrated in weekly fixed increments during the first 6 weeks up to a maximum of oxycodone 40 mg plus naloxone 20 mg. The mean daily dose of oxycodone/naloxone was 21.9/11.0 mg, and placebo oxycodone equivalent 34.4 mg/19.4 mg. Improvement in mean IRLS rating scale score at 12 weeks was significantly greater in the treatment group (-16.6 points) vs the placebo group (-9.5 points). This beneficial effect was also maintained throughout an open-label, 40-week extension phase. Treatment-related adverse events included fatigue, constipation, nausea, and headache, and serious adverse events included severe constipation in two patients, one case of ileus, and one case of vomiting. There were three cases of drug withdrawal symptoms. Most quality-of-life measures were also significantly improved with oxycodone/naloxone at the end of the double-blind phase.

■ COMMENTARY

This study provides strong evidence that prolonged-release oxycodone-naloxone is effective and well tolerated in the treatment of severe RLS, in cases in which standard treatments have failed. The majority of individuals in the treatment arm experienced at least a 50% decrease in severity rating scale scores, and more than 40% achieved scores in the mild RLS range. Dopaminergic medications are generally used as first-line treatment in patients with RLS, but in the long-term can lead to loss of efficacy and augmentation of symptoms. Moreover, they are not well tolerated in some patients, and even at low doses used for RLS treatment, dopamine agonist-associated impulse control disorders have been reported. Gabapentin enacarbil is approved for RLS treatment, but again some patients experience refractory and troublesome symptoms. There remains, therefore, a critical need for alternatives. In such situations, off-label choices include gabapentin, pregabalin, benzodiazepines, and opioids such as oxycodone and methadone. Opioids have long been used for RLS, with recording of the opiate laudanum use for RLS as early as the 17th century. However, there has been very little evidence from clinical trials to support their use, and the majority of studies have been open-label. This clinical trial, therefore, adds considerably to RLS treatment, and should stimulate further studies. In particular, it would be interesting to see how the benefit of prolonged-release oxycodone-naloxone stacks up against more familiar treatment options, including dopamine agonists and gabapentin enacarbil. There are also particular challenges to using opiates for treatment. There is concern about development of tolerance, and, although the open-label extension in the study supports sustained benefit, longer-term data would be helpful. Drug dependence and addiction is another concern, although in this study only three cases in which withdrawal symptoms occurred were noted. There is the risk of opioid-related bowel dysfunction including severe constipation, but this fixed-dose combination of prolonged-release oxycodone-naloxone has been shown in previous studies for pain to be significantly more tolerable in terms of bowel function when compared to oxycodone. As yet, it remains unclear whether opioids will cause less augmentation of RLS than

Continued on page 46

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*

Transient Visual Symptoms — A Special Subset of Transient Ischemic Attacks

Source: Lavallée PC, et al. Spectrum of transient visual symptoms in a transient ischemic attack cohort. *Stroke* 2013;44:3312-3317.

Transient visual symptoms (TVS) are common complaints that often prompt patients to seek attention in hospital emergency departments, or urgent visits with ophthalmologists and neurologists. Sometimes they are rapidly identified as transient ischemic attacks (TIAs), but at other times they are misdiagnosed and a significant delay occurs prior to diagnosis. The investigators in this study run a specialized TIA clinic in Paris, and they described their experience with TVS in a large cohort of patients who were evaluated for TIAs.

The study included 826 patients (34% of the entire TIA cohort) who had TVS, including 422 (17.6%) patients with isolated TVS. These were part of a cohort of 2398 patients with suspected TIAs evaluated from 2003 through 2008. The most frequent symptom was transient monocular blindness in 36.3%, followed by diplopia in 13.4%, homonymous lateral hemianopia in 12.3%, bilateral positive visual phenomenon in 10.8%, and lone bilateral blindness in 4.5%. All patients underwent intensive neurovascular investigation, including brain imaging with CT and/or MRI, and evaluation of the extracranial and intracranial arterial circulation with either ultrasound and transcranial Doppler, or MR angiography and CT angiography. Cardiac investigations included ECG and echocardiography. Vascular risk factors were systematically identified and reported, and the diagnosis was then made of TIA, with or without recent brain infarct on imaging. Major findings were defined as those that could lead to short-term risk of recurrent stroke, and included symptomatic intracranial or extracranial atherosclerotic stenosis ≥ 50%, cervical artery dissection, and a major source of cardiac embolism.

Positive diffusion-weighted MR imaging was found in 11.8% of patients with homonymous hemianopia, and 5% of patients with transient monocular blindness. When comparing patients with TVS to those with other neurological symptoms of a TIA, patients with visual symptoms were less likely to have a major source of cardiac or arterial embolism than patients with cerebral or brainstem neurological symptoms (19.6% vs 28.1%; $P < 0.001$). However, the investigators found a higher rate of atrial fibrillation in patients who presented with homonymous hemianopia (23.2%) than patients with other types of TVS (4.0%, adjusted odds ratio, 6.71). Although patients with TVS have an overall lower rate of serious underlying arterial pathology than those with other neurological symptoms, there is still a high prevalence of atrial fibrillation and these patients should be treated emergently as all other patients with TIAs. ■

Childhood Ischemic Stroke Is a Rare but Important Problem

Source: Mallick AA, et al. Childhood arterial ischaemic stroke incidence, presenting features, and risk factors: A prospective population-based study. *Lancet Neurol* 2014;13:35-43.

Childhood stroke is an unusual event that is difficult to study because of its very low prevalence in the general population. Investigators in Southern England, which has a population of 5.99 million children, undertook a prospective identification of all cases of arterial ischemic stroke that occurred in children from the age of 29 days to < 16 years, during one 12-month period (July 2008-June 2009). They identified cases using multiple sources, including pediatric neurologists and trainees, general pediatricians, radiologists, physical therapists, neurosurgeons, and parents. The cases were confirmed by personal examination and recorded notes, and details of the presenting features, risk factors, and diagnostic investigations were recorded and analyzed.

The investigators identified 96 cases of childhood arterial ischemic stroke, resulting in a crude incidence of 1.60 events per 100,000 children per year. The incidence was highest in children < 1 year of age. There was no difference in the risk of arterial ischemic stroke between sexes, but there was a higher relative risk in Asian children (relative risk [RR], 2.14) and in black children (RR, 2.28) compared to whites. Eighty-five percent of the children presented with focal neurological features, most commonly hemiparesis. Seizures were more common in the younger children < 1 year of age, and headache was more common at presentation in older children > 5 years of age. At least one risk factor for arterial ischemic stroke was identified in 83% of the cases. The most common underlying risk factors were

acute systemic illness in 31%, often represented by systemic infections, arteriopathy in 29%, and chronic systemic illnesses in 25%, as represented by sickle cell disease and hematologic disorders. A cardiac anomaly, which might explain cardiogenic embolism, was present in 23% of the children, and acute injuries to the head and neck were present in 19% of the children. Less common risk factors were prothrombotic states, and what are considered "adult" atherosclerotic risk factors, such as high cholesterol or hypertension, were infrequent.

Childhood arterial ischemic stroke is rare and does not share many of the risk factors that are present in adults. Age and race affect the risk to a significant degree, but not sex. Further investigation of causes, and long-term follow-up to assess the outcomes in these patients, will be important to fully understand this syndrome. ■

Lower Cerebral Vasomotor Reactivity is Associated with Increased Mortality

Source: Portegies ML, et al. Cerebral vasomotor reactivity and risk of mortality: The Rotterdam study. *Stroke* 2014;45:42-47.

Cerebral vasomotor reactivity is a term that describes the development of stiffness and loss of autoregulatory responses in the cerebral arteries and arterioles. It is determined in a noninvasive way by measuring transcranial Doppler velocity of the middle cerebral arteries and measuring the change in velocity with the inhalation of 5% carbon dioxide. It is a test that has been used for decades to evaluate patients for risk of stroke when there is a proximal artery stenosis that is being considered for revascularization. In the current study, the investigators were not evaluating an arterial stenosis, but were looking at the general cerebral vasomotor reactivity of arteries throughout the brain.

The investigators studied 1695 participants of the Rotterdam study during the years 1997 through 1999. The Rotterdam study is a population-based cohort study looking at cardiovascular risk factors and cardiovascular events in a defined population. In this study, cerebral vasomotor reactivity was measured as noted above, and was correlated with mortality using Cox proportional hazards models, with adjustments for age, sex, and blood pressure changes, and subsequently for other cardiovascular risk factors.

In the fully adjusted model, the participants in the study had an increased mortality, with a hazard ratio per standard deviation decrease in vasomotor reactivity of 1.10 for all-cause mortality, 1.09 for cardiovascular mortality, and 1.10 four non-vascular mortality. Patients who had incidence stroke were excluded but the associations remained unchanged.

These investigators found that lower cerebral vasomotor reactivity is associated with an increased risk of death. Incidence stroke did not effect this association, and suggests that the effects are mediated through an impaired vascular system in all of its manifestations. This noninvasive test can be used as part of a series of vascular physiological studies that may identify patients who are at high risk for cardiovascular death, with the hope that interventions can reduce those risks. ■

Multiple Cervical Artery Dissections — Presentation and Etiology

Source: Béjot Y, et al. Characteristics and outcomes of patients with multiple cervical artery dissection. *Stroke* 2014;45:37-41.

Cervical artery dissection is an important cause of ischemic stroke in young adults. In various series of cervical artery dissections, multiple cervical arteries are involved and account for 13- 28% of overall cervical artery dissection cases. Little is known about the factors contributing to multiple artery dissections as well as its prognosis. Béjot et al looked at the baseline characteristics and short-term outcomes of patients with single artery dissections and multiple artery dissections to determine if there were significant differences between the groups.

The authors enrolled 983 patients with a diagnosis of cervical artery dissection in centers from eight different countries, including Argentina, Belgium, Finland, France, Germany, Italy, Switzerland, and Turkey. Patients were recruited either prospectively or retrospectively from local registries and artery dissection was defined by the presence of a mural hematoma, aneurysmal dilation, long tapering stenosis, intimal flap, double lumen, or occlusion > 2 cm above the carotid bifurcation revealing an aneurysmal dilatation or long tapering stenosis after recanalization of a cervical artery. Pure intracranial dissections and iatrogenic dissections were excluded. Among the 983 patients, 149 (15.2%) presented with multiple cervical artery dissections. Multiple dissections were more often associated with cervical pain at time of admission (odds ratio [OR], 1.59),

a remote history of head or neck surgery (OR, 1.87), a recent infection (OR, 1.71), and cervical manipulation (OR, 2.23). On imaging, fibromuscular dysplasia or the presence of a pseudoaneurysm was more often seen in patients with multiple dissections. However, the presence of multiple dissections rather than a single dissection had no effect on recovery or functional outcome at 3 months.

In this large series of patients with cervical artery dissections, the authors noted significant differences between multiple and single artery involvement. Features suggestive of an underlying vasculopathy, such as fibromuscular dysplasia, and environmental triggers, such as recent infection, cervical manipulation, and a remote history of head or neck surgery, were preferentially associated with multiple cervical arterial dissections area. ■

Continued from page 43

dopaminergic intervention, but that is a possibility which needs to be examined. In summary, this important clinical trial provides hope for carefully chosen individuals with severe RLS in which standard treatments have either not worked or not been tolerated. ■

Inhaled Apomorphine as a Rescue Treatment in Parkinson's Disease

ABSTRACT & COMMENTARY

By Alexander Shtilbans, MD, PhD

Assistant Professor of Neurology, Weill Cornell Medical College

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

Synopsis: *Inhaled apomorphine, at doses up to 0.8 mg, appears safe and well tolerated by patients with Parkinson's disease, but does not result in significant improvement in wearing "off" periods, at the tested doses.*

Source: Grosset KA, et al. Phase IIa randomized double-blind, placebo-controlled study of inhaled apomorphine as acute challenge for rescuing "off" periods in patients with established Parkinson's disease. *Eur J Neurol* 2013;20:1445-1450.

Parkinson's disease causes severe motor symptoms — rigidity, bradykinesia, resting tremor, and postural instability. The motor symptoms respond to dopaminergic therapies such as dopamine agonists or levodopa. However, after several years of treatment, some patients develop motor fluctuations, such as dyskinesias and wearing "off" episodes. Young patients and those taking high doses of levodopa are more prone to developing dyskinesias. Wearing "off" is a troubling symptom that occurs at the end of the active period of a levodopa dose, and in some cases at any time. Presently, there are no safe and effective non-parenteral, FDA-approved, rapid-acting treatments to modify these episodes. Apomorphine, a potent dopamine agonist, has been studied as a rescue medication for wearing "off" episodes. When injected subcutaneously, however, it may cause severe nausea, vomiting, and skin reactions. Therefore, alternative routes of administration are being sought.

The authors of this paper conducted a single-center, randomized, double-blind, placebo-controlled study of the inhaled formulation of apomorphine for rescue treatment during "off" periods in patients with Parkinson's disease. The study aimed to find the minimum efficacious dose of inhaled apomorphine, as well as evaluate the safety, tolerability, and pharmacokinetics of this drug. Three different doses of apomorphine were compared to placebo. Parkinson's disease subjects had the disease for at least 3 years, complicated by motor fluctuations, and were in Hoehn and Yahr stage 2 to 2.5. Three dosage arms tested inhaled apomorphine doses of 0.2 mg, 0.5 mg, and 0.8 mg. Each arm included six patients receiving the drug and two receiving placebo. The primary endpoint was the proportion of patients who reported being in an "on" state at any time after dosing, and the time to improvement from "off" to "on." The secondary endpoint was the duration of the "on" state after dosing. Other outcomes measured were the change in the UPDRS 3 upper limb score, before and after dosing. Demographic characteristics of the patients within the three groups were comparable, except for the group receiving 0.8 mg of apomorphine, who were all males. The proportion of patients in the "on" state after receiving the drug was 0% at 0.2 mg, 50% at 0.5 mg, and 33.3% at 0.8 mg. One-sixth (16.7%) of patients receiving placebo achieved the "on" state ($P = 0.1311$). The mean duration of "on" time after dosing was 10 minutes for the 0.2 mg dose, and 40 minutes for 0.5 mg and 0.8 mg of apomorphine. Placebo was associated with 20 minute-mean duration of "on" time. The changes in UPDRS 3 were not significantly different between the active drug groups and placebo. Dyskinesias were not observed. Inhaled apomor-

phine was rapidly absorbed, achieving peak blood concentration at 1-3 minutes. The most common side effects for apomorphine and the placebo groups were headache and paresthesias.

The authors concluded that the inhaled formulation of apomorphine, at the doses studied, was well tolerated, but the small sample size limited the interpretation of the efficacy data of the study, which was not significantly different from placebo.

■ COMMENTARY

This is the first trial that evaluated the inhaled formulation of apomorphine and showed that it has high bioavailability, making it a potentially good rescue medication. However, the number of trial subjects was small and the group of patients receiving the highest dose of the drug was entirely male. There was a suggestion of efficacy at the highest dose of apomorphine tested (0.8 mg), but this was not significantly different from the placebo effects. Therefore, it will be important to test the drug in a larger group that includes women. The authors enrolled patients with a Hoehn and Yahr score of 2 to 2.5, which represents a moderate stage of disease, and would exclude some patients with more severe motor complications, including "off" periods. Only upper limbs were evaluated, limiting the assessment of patients with lower body-predominant Parkinson's disease.

The lack of significant adverse events or serious side effects, including nausea and vomiting, is encouraging and warrants further studies of inhaled apomorphine at higher doses and in a larger and more diverse group of patients. ■

Height and Bone Age in Treated Juvenile Myasthenia Gravis

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: *In young children with myasthenia gravis, height and bone age are negatively impacted by chronic corticosteroid usage, but not by thymectomy.*

Source: Wang H, et al. The effect of steroid treatment and thymectomy on bone age and height development in juvenile myasthenia gravis. *Neurol Sci* 2013;34:2173-2180.

Treatment of juvenile myasthenia gravis (MG) mirrors that of adult-onset disease, with first-line agents, all of temporary benefit, encompassing anticholinesterase medication, plasmapheresis, and intravenous immune globulin. Thymectomy, widely accepted for both seropositive and seronegative patients, both peri- or post-pubertal, remains controversial in the pre-pubertal child, and glucocorticoids, though problematic for chronic use, are administered for severe disease. Thymectomy is not beneficial for MuSK antibody-positive adult or juvenile MG, but azathioprine, mycophenolate mofetil, cyclosporine, and cyclophosphamide, despite risks of infertility and delayed malignancy, are beneficial. What are the risks to bone age and height development in such treated children?

Among 76 consecutive juvenile MG patients treated between July 2011 and August 2012 in the outpatient clinic of the First Affiliated Hospital of Sun Yatsen University, China, and enrolled into this cross-sectional study, 52 had undergone thymectomy and 71 had received prednisone. All satisfied diagnostic criteria for juvenile MG, including age < 18 years, muscle fatigability which improved with rest, and one of either abnormal jitter on single-fiber electromyography, decrement of 10% on repetitive nerve stimulation, or positive response to anticholinesterase. Exclusionary criteria included bulbar MG, other autoimmune disease, congenital or neonatal MG, thymoma, or any disease that might impair growth or metabolism. Statistical analysis encompassed *t* tests and variance analyses, and Chi square and Rank sum tests, with $P < 0.05$ considered statistically significant.

Among 76 juvenile MG patients, 45 female and 31 male, median age was 10.3 years, median onset age was 4.8 years, and 62 (82%) were purely ocular with 18% generalized. Treatment was not significantly different between the sexes. Among the 52 thymectomized children, bone age was not delayed, and bone growth and height were not impacted, by the duration or presence of thymectomy. Height retardation *was* related to past cumulative prednisone intake, as was delayed bone age, which was also impacted by age of onset, with delayed bone age more pronounced the earlier the age of onset. Bone age and height are negatively affected by prednisone but not by thymectomy, and monitoring of these parameters should be routine in juvenile MG, with intervention, particularly the use of steroid-sparing agents, undertaken when appropriate.

■ COMMENTARY

Recently, a coincidence of two rare diseases, seropositive MG and aquaporin-4 antibody-mediated neuromyelitis optica spectrum disorder (NMOSD), has been described in 16 patients, an occurrence 70 times more frequent than would be expected by chance.[1] Most were female (15/16), and Caucasian (11/16), with MG onset prior to NMOSD onset (14/16), the former of which was usually mild, and

mostly developing within the first 3 decades of life (12/16) of which 11/12 were female, with many in remission or having only minimal manifestations (11/16). Of those with MG onset prior to neuromyelitis optica onset (14/16), 10/11 had undergone thymectomy prior to NMOSD onset. NMOSD appears to develop almost exclusively in females with juvenile or early-onset MG, and prior thymectomy may be a risk factor in its development. ■

Reference

1. Leite MI, et al. Myasthenia gravis and neuromyelitis optica spectrum disorder: A multicenter study of 16 patients. *Neurology* 2012;78:1601-1607.

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.

CME Questions

1. In a recent study of cEEG in ICU patients, Ney et al reported all of the following *except*:
   a. There was a significant increase in cEEG utilization over time.
   b. cEEG monitoring was associated with a significantly longer length of stay when compared to routine EEG.
   c. cEEG monitoring was associated with improved inpatient survival when compared to routine EEG.
   d. cEEG monitoring was associated with younger patient age compared to routine EEG.

2. What are potential advantages of prolonged release oxycodone-naloxone over dopamine agonist treatment for restless legs syndrome (RLS)?
   a. Fewer gastrointestinal side effects
   b. A larger body of clinical trial data supporting its use
   c. No reports of drug withdrawal symptoms
   d. Efficacy in relieving RLS symptoms in cases where dopamine agonists have proved ineffective
   e. No side effect of fatigue

3. Inhaled apomorphine has been demonstrated to be safe and effective in the treatment of end-of dose "off" periods in patients with Parkinson's disease?
   a. True
   b. False

4. Which of the following statements is *true* regarding myasthenia gravis?
   a. Bone age and height are negatively affected by prednisone but not by thymectomy.
   b. Bone age but not height is negatively affected by prednisone but not by thymectomy.
   c. Bone age and height are negatively affected by prednisone and by thymectomy.
   d. Bone age and height are positively affected by prednisone but not by thymectomy.
   e. Bone age and height are positively affected by prednisone and by thymectomy.

5. Patients who present with transient visual symptoms should be evaluated and treated in the same way as all patients with TIAs.
   a. True
   b. False

6. Childhood arterial ischemic stroke is associated with the same risk factors that are associated with ischemic stroke in adults.
   a. True
   b. False

7. Cervical artery dissections may be single or multiple, and there are no differences in underlying pathophysiology, or risk factors.
   a. True
   b. False

In Future Issues:

Update on Sleep Disorders