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.

Hyperbaric Oxygen Therapy for Blast-related Postconcussion Syndrome: Does It Work?

ABSTRACT & COMMENTARY

By Nitin K. Sethi, MD

Assistant Professor of Neurology, Weill Cornell Medical College

Dr. Sethi reports no financial disclosures relevant to this field of study.

Synopsis: *This well-designed, randomized, controlled trial, which included a sham arm, showed no evidence for the efficacy of hyperbaric oxygen therapy to treat the symptomatic, cognitive, and behavioral sequelae of postconcussion syndrome in soldiers after combat-related mild traumatic brain injury.*

Source: Cifu DX, et al. Hyperbaric oxygen for blast-related postconcussion syndrome: Three-month outcomes. *Ann Neurol* 2014;75:277-286.

BLAST-RELATED MILD TRAUMATIC BRAIN INJURY (TBI) HAS BEEN RECOGNIZED as the "signature injury" of America's global war on terrorism in Iraq and Afghanistan. The Military Acute Concussion Evaluation test is increasingly identifying mild TBI and postconcussion symptoms (PCS), such as headaches, dizziness, balance problems, problems with concentration and memory, and behavioral and personality changes, in soldiers post exposure to a blast from an improvised explosive device. There is in-

Pharmacology Watch, *Clinical Briefs* Available Online

The May 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 9 • MAY 2014 • PAGES 65-72

NOW AVAILABLE ONLINE
www.ahcmedia.com

creasing concern about the long-term health consequences in these soldiers and concussion management algorithms have been developed for use both on the battlefield and in the garrison setting. Hyperbaric oxygen therapy (HBO2T), which refers to the therapeutic administration of 100% oxygen at environmental pressures > 1 atmosphere absolute (ATA), has been used as a treatment for mild TBI and PCS, but its efficacy has never been proven in appropriate clinical trials.

In this study, Cifu et al investigated the use of HBO2T to treat mild TBI and PCS in 61 male Marines. Forty once-daily, 60-minute hyperbaric chamber compressions at 2.0 ATA were given at one of three randomly preassigned oxygen fractions, resulting in the Marines being randomly assigned to one of the three groups with an oxygen-breathing exposure equivalent: 1) surface air (sham group), 2) 100% oxygen at 1.5 ATA, or 3) 100% oxygen at 2.0 ATA. The Rivermead Post-Concussion Questionnaire-16 (RPQ-16) was applied before treatment and 2 months after treatment to assess outcome of HBO2T. Unfortunately, the trial showed no significant differences between the groups, and no evidence of efficacy at 3 months post compression in treating the symptomatic, behavioral, or cognitive sequelae of PCS after mild TBI.

■ COMMENTARY

Mild TBI and PCS are being increasingly recognized, both in the military and civilian (sports) setting. Patients usually present with a constellation of symptoms following mild closed TBI. Concussion identification algorithms aid timely identification and management of mild TBI and concussions, both on the battlefield and in the civilian arena. Treatment at present is conservative and includes removal from the battle or the sport field, reduction of environmental stimuli, pharmacological management of headache, and a mandatory recovery period until total symptom resolution. The ongoing international conflicts have resulted in an increasing number of soldiers returning from the battlefield with mild TBI and PCS, creating a public health issue, and there is an acute need for more effective interventions. HBO2T (at pressures between 1-3 ATA) has been proposed to aid recovery in TBI patients by reducing intracranial pressure, improving tissue oxygenation and cellular metabolism, anti-apoptotic effects, immune modulation, reactivation of damaged but functional neuronal circuits, neurotransmitter modulation, and stem cell mobilization.[1,2] A Cochrane review in 2004 concluded that while the adjunctive use of HBO2T in TBI patients may reduce the risk of death and improve the final Glasgow Come Scale, survivors failed to achieve a good outcome and many were left with severe disability.[3] A concern for pulmonary impairment was further raised in the HBO2T treated patients. At the present time, evidence for effectiveness is conflicting and the routine application of HBO2T in these patients is not justified. Further studies in animal models of TBI and humans, including dose-ranging and safety studies, are needed. ■

References

1. McDonagh MS, et al. Hyperbaric oxygen therapy for brain injury, cerebral palsy, and stroke. *Evid Rep Technol Assess* (Summ) 2003 Sep;(85):1-6.
2. Huang L, Obenaus A. Hyperbaric oxygen therapy for traumatic brain injury. *Med Gas Res* 2011;1:21.
3. Bennett MH, et al. Hyperbaric oxygen therapy for the adjunctive treatment of traumatic brain injury. *Cochrane Database Syst Rev* 2012;12:CD004609.

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.
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.

Baseline Impairments and Decline in Cognition in Early 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: *The Montreal Cognitive Assessment and Mini-Mental Status Exam demonstrated baseline deficits in early Parkinson's disease. Male sex, motor, and non-motor measures including depression and hyposmia were associated with cognitive dysfunction.*

Source: Hu MT, et al. Predictors of cognitive impairment in an early stage Parkinson's disease cohort. *Mov Disord* 2014;29:351-359.

This study focused on clinical rating scales measuring cognitive function in individuals with Parkinson's disease (PD) followed in the "Oxford Discovery Cohort," all within 3.5 years of diagnosis. Baseline data were compared with 144 healthy controls, and longitudinal data over 18 months were available for 155 PD subjects. PD subjects were slightly older than controls (67.8 ± 9.4 vs 63.5 ± 8.9 years; $P < 0.001$), with less education (13.6 ± 3.5 vs 15.1 ± 3.5 years; $P < 0.001$), and were more likely to be men (61.3% vs 35.5%). Mean PD duration was 1.5 ± 1.0 years, motor Unified PD Rating Scale (UPDRS) score was 26.8 ± 11.0, and Hoehn and Yahr score was 1.9 ± 0.5, all reflecting early stage PD. There was a significant reduction in PD compared with controls at baseline in Modified Mini-Mental Status Examination (MMSE) scores (27.3 ± 2.2 vs 28.4 ± 1.8, respectively; $P = 0.001$), and Montreal Cognitive Assessment (MoCA) scores (24.9 ± 3.5 vs 27.1 ± 2.2, respectively; $P < 0.001$). Using diagnostic thresholds for the MMSE, 7.2% of PD subjects had either PD-Mild Cognitive Impairment (PD-MCI) or PD-Dementia (PDD) compared with just 1.4% of controls. However, MoCA scores using diagnostic thresholds found 14.2% with PD-MCI and 16.3% with PDD in the PD group, vs 6.4% and 0.7%, respectively, in the control group. Strong predictors of worse MoCA scores in the PD group at baseline included older age, male sex, and fewer educational years. Multivariable linear regression analysis also revealed a number of motor and non-motor features associated with MoCA scores: Hoehn and Yahr stage; annualized UPDRS score; Timed Up and Go test; balance, anxiety, and depression rating scales; and hyposmia. Only MoCA scores significantly declined over 18 months follow-up in the PD group (from 25.7 ± 3.0 to 24.9 ± 3.4; $P < 0.001$), with a shift from normal to PD-MCI in 33 subjects (21.3%), and from PD-MCI to PDD in 7 subjects (4.5%). Only 51 (32.9%) remained in the normal range. Changes were driven by subscores for memory, orientation, and semantic fluency.

■ COMMENTARY

The occurrence of cognitive impairment in early PD has been well established over the last few years, and Movement Disorder Society Task Force guidelines on PD-MCI were published in 2012. However, detailed understanding of its heterogeneity, impact, progression, and associations is lacking. This study, therefore, moves the field ahead in using prospectively collected data in a well-characterized PD cohort. In this early PD population, the investigators found that PD-MCI was common, but using MoCA scores at diagnostic thresholds, 16.3% of this early PD cohort were already classified as having PDD. As much as the initial diagnostic data are alarming, so is the longitudinal aspect of the study. Almost 26% of patients progressed across MoCA cutoff values used for classification. This suggests that we should be following our patients in clinic using MoCA ratings, even in early PD. Where does the MMSE fit into patient assessment? MMSE classification at diagnostic thresholds found fewer PD-MCI and PDD scores; the authors suggest this is due to lower sensitivity of the MMSE, although they acknowledge that it may also be due to over-classification of MCI and PDD by MoCA scores. MMSE longitudinal changes over 18 months were also difficult to explain: 24% of PD subjects deteriorated but 25% improved, suggesting a degree of misclassification. Although the present study suggests using the MoCA scale will be more helpful as a short "clinic-friendly" tool to follow cognition in PD, it remains difficult to reconcile data with a recent publication in the same journal by Lessig et al.[1] These investigators found that MMSE but not MoCA significantly declined over a time span of 3 years. Hu and colleagues suggest this is due to a difference in disease duration between the two studies, and that MMSE might be more sensitive in later PD. In the end, it will take further follow up and careful clinical evaluation to clarify how well the MoCA and MMSE scores in this study correlate with clinical diagnosis, and the finding of PDD in this cohort raises the question of diagnostic accuracy within the cohort.

Nonetheless, in addition to providing valuable information on use of these brief bedside tests in early PD, the study identified a number of interesting associations with cognition, among them male sex. This, therefore, adds to a growing literature on sex differences in PD presentation. Worse motor function and olfaction were also associated with worse cognitive measures. Whether these have specific neurochemical underpinnings in common, such as cholinergic involvement, or whether cognitive deficits reflect more "global" pathology remains to be seen. This study supports use of a simple tool in the clinic, that when better described, may aid in assessing prognosis and tracking disease progression: both of which are critical and unmet needs. ■

Reference

1. Lessig S, et al. Changes on brief cognitive instruments over time in Parkinson's disease. *Mov Disord* 2012;27:1125-1128.

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*

Hemicraniectomy in Older Patients with Large Middle Cerebral Artery Infarcts Reduces Mortality

Source: Juttler E, et al, for the DESTINY II Investigators. Hemicraniectomy in older patients with extensive middle-cerebral-artery stroke. *N Engl J Med* 2014;370:1091-1100.

In an earlier study of early decompressive hemicraniectomy for large middle cerebral artery strokes, the same investigators demonstrated reduced mortality without increasing the risk of very severe disability among patients ≤ 60 years of age. These investigators now report the results of a similar trial in 112 patients, ≥ 61 years of age (mean age 70 years; range 61-82) who were randomized to either hemicraniectomy within 48 hours or conservative treatment in the intensive care unit. The primary endpoint was survival without severe disability, defined as a modified Rankin score of 0 to 4.

Hemicraniectomy improved the primary outcome, with the proportion of patients who survived without severe disability being 38% in hemicraniectomy group, compared to 18% in the control group. This result was a direct result of a lower mortality in the surgical group, and no difference between the groups in the degree of severe disability. The results of this trial in an older age group is quite similar to what was found in younger patients, and this procedure therefore remains an option for patients of all ages. However, patients and families should be made aware that a successful hemicraniectomy may improve survival, but it will not improve neurological recovery. ■

Sleeping Pills Increase Risk of Death

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: *Chronic use of sleeping medications, particularly benzodiazepines, is associated with an increase in all-cause mortality, and should be avoided if at all possible.*

Source: Weich S, et al. Effect of anxiolytic and hypnotic drug prescriptions on mortality hazards: Retrospective cohort study. *BMJ* 2014;348:g1996 doi:10.1136/bmj.g1996.

Poor sleep may have serious health consequences. Both insomnia and short sleep duration have been associated with increased mortality as well as cognitive decline. Hypnotic and anxiolytic drugs have been associated with an increased risk of dementia, daytime fatigue, ataxia, falls, and traffic accidents. Medical ailments such as cancer, pneumonia, and other infections have been associated with use of these medications.

Prior studies have varied in setting, age distribution, and length of follow up. These studies have also been inadequately controlled for physical and psychiatric confounding variables. Use of other medications, socioeconomic status, smoking, and drug and alcohol misuse have also possibly confounded previous studies. These studies have also shown wide variations in their effect size, with mortality hazard ratios varying from 1.14 to 4.56. In the present study, the use of sedative hypnotic medications (primarily benzodiazepines and non-benzodiazepine GABA agonists — the so-called Z-drugs) were found to be associated with a significantly increased risk of death. The Z-drugs (zolpidem, zopiclone, and zalephon) are the most commonly prescribed medications for insomnia in the United States.

This large population cohort, enrolled between 1998 and 2001 from primary care practices in the United Kingdom, was studied for an average of 7.6 years. There were 34,727 patients prescribed anxiolytic or hypnotic drugs. These were matched with 69,418 patients with no prescriptions for these drugs. Matching included age, sex, and practice location, which was important in excluding differences in socioeconomic status.

Physical and psychiatric comorbidities were significantly more prevalent among those prescribed study drugs than among controls. Patients on study drugs were more likely than controls to be current smokers and had higher rates of all forms of disorders such as cancer and respiratory disease. Study drug users not unexpectedly had a higher incidence of sleep disorders, anxiety, and other psychiatric

Stroke Alert: A Review of Current Clinical Stroke Literature

Blood Pressure Variability May Predict Poor Outcome After Intracerebral Hemorrhage

Source: Manning L, et al, for the INTERACT2 investigators. Blood pressure variability and outcome after acute intracerebral haemorrhage: A post-hoc analysis of INTERACT2, a randomized controlled trial. *Lancet Neurol* 2014;13:364-373.

INTERACT2 WAS A STUDY OF THE IMPACT OF TWO BLOOD pressure treatment protocols in patients with spontaneous intracerebral hemorrhage. In that study, two groups were randomly assigned, one group with a target systolic blood pressure < 180 mmHg, and the other group with a target systolic blood pressure of < 140 mmHg. The initial phase of that study showed that there was no difference in neurological outcome, and recommendations were made to target the lower systolic blood pressure values.

This post-hoc analysis of the variability of systolic blood pressure looked at the standard deviation of systolic blood pressure during five measurements taken in the first 24 hours (hyperacute phase) and during 12 measurements taken over days 2-7 (acute phase).

Analysis of the variability of systolic blood pressure indicated that patients who had the highest adjusted quintile of standard deviation of systolic blood pressure in the hyper acute phase, or the acute phase, had an elevated odds ratio (1.41; $P = 0167$) of poor outcome, determined by major disability at 90 days. The authors suggest that outcomes might be improved if there was a smooth and stable reduction of blood pressure in the first several days after intracerebral hemorrhage, avoiding excessive variability and rebounds of systolic blood pressure. ■

disorders. They received more prescriptions for non-study drugs. Controlling for these factors, the mortality hazard ratio for any use of study drug during the first year after recruitment was 3.32 (95% confidence interval [CI], 3.19-3.45). There was a positive dose response for all three classes of study drugs, with a hazard ratio of 4.51 (CI, 4.22-4.55) for patients who received > 90 defined daily doses of drug in the first year. There were approximately four excess deaths linked to drug use per 100 people followed. Benzodiazepines had higher hazard ratios than other study drugs.

Benzodiazepines (n = 22,116; 63.7%) were more commonly prescribed than Z-drugs (n = 7971; 23%). Other study drugs (most commonly hydroxyzine, buspirone, or promethazine) were prescribed in n = 4640 (13.4%). Of note, the study could not account for the use of other sleep aids, available over the counter, such as diphenhydramine. The most commonly prescribed drug was diazepam, followed by temazepam and zopiclone. Co-prescribing was common, with 30% of patients using more than one agent.

■ COMMENTARY

This study is impressive in its size and scope. It included more than 70 million patient years of high-quality, validated data. As the authors note, this study measured hypnotic drug use as a function of written prescriptions rather than patient-reported use. The validity of this method was strengthened by the exclusion of patients with single study drug prescriptions, thus focusing on those patients who required repeated follow-up prescriptions. Medications given to psychiatric patients directly by mental health providers would not be accounted for, but in the United Kingdom, the vast majority of medication is prescribed through primary care physicians.

Studies such as this are susceptible to significant confounding bias. As the authors note, however, very detailed health information was available for this population. This reduced the effect of drugs being given to those with preexisting serious illness or those not able to sleep because of pain or other consequences of long-term or life-threatening illness.

It is important to note that this was not a dedicated sleep study. Psychiatric disease was very common in this population: 15,299 (44%) had an anxiety disorder and 19,770 (56.9%) had other psychiatric diagnoses. By contrast, only 9741 (28.2%) patients had a sleep disorder. It is not clear from the manuscript exactly how sleep disorders were diagnosed, as this group may have not only included insomniacs but others with circadian rhythm disorders, parasomnias, and possibly obstructive sleep apnea.

Because of this psychiatric predominance and possibly because of different prescribing practices in the United Kingdom, this study was strongly tilted toward benzodiazepines, rather than Z-drugs. However, as noted in the paper, the ill effects of Z-drugs and other hypnotics were still significant, with hazards ratios of 3.68, 3.19, and 2.06 for benzodiazepines, Z-drugs, and other study drugs, respectively.

The study did not have the ability to make conclusions about the cause of the increased mortality since the cause of death was not included in the database. Cause of death can be a difficult variable to analyze, since death certificates often list diagnoses such as pneumonia or heart failure, while the true cause of death may have been cancer or any other chronic progressive disorder. No information is available regarding accidents or other effects of excessive daytime sleepiness.

This study argues strongly for behavioral over pharmacological approaches to insomnia and anxiety. Drug therapy in the form of benzodiazepines, Z-drugs, or even seemingly "benign" medications such as hydroxyzine is associated with a significantly increased risk of death. ■

B-lymphocyte Targeted Therapies for MS — Paradoxical Effect of Atacicept

ABSTRACT & COMMENTARY

By Jai S. Perumal, MD

Assistant Professor of Neurology, Weill Cornell Medical College

Dr. Perumal is on the speakers bureau for Biogen Idec, Teva Pharmaceuticals, Genzyme Corp., and Acorda Therapeutics.

Synopsis: *A Phase 2 trial of atacicept, a humanized recombinant protein that suppresses B cell function, demonstrated a negative impact on clinical disease activity in relapsing-remitting multiple sclerosis.*

Source: Kappos L, et al. Atacicept in multiple sclerosis (ATAMS): A randomized, placebo-controlled, double-blind, phase 2 trial. *Lancet Neurol* 2014;13:353-363.

The traditional view regarding the pathogenesis of multiple sclerosis (MS) postulated a T-cell mediated disease, but several lines of evidence now point to a significant role of B-lymphocytes in the pathogenesis of MS. B-cell targeted therapies such as rituximab, which is an anti-CD20 monoclonal antibody, have demonstrated high efficacy for suppression of inflammatory injury in MS as evidenced by a beneficial effect in reducing relapses and MRI lesions. Ocrelizumab, a humanized anti-CD20 monoclonal antibody, is currently in Phase 3 trials for MS. Studies showing a prominent role for B-cells in the immunopathogenesis of MS and the established efficacy of prior B-cell targeted therapies provided the rationale for exploring atacicept, which is a recombinant protein that suppresses B-cell function, for the treatment of MS. Atacicept binds to and blocks B-lymphocyte stimulator and a proliferation-inducing ligand, which serve key functions in B-cell maturation and survival. Atacicept was specifically designed for the treatment of autoimmune diseases including systemic lupus erythematosus and rheumatoid arthritis and is being explored for those indications as well.

Atacicept in Multiple Sclerosis (ATAMS) was a randomized, double-blind, placebo-controlled, 36-week, Phase 2 trial to assess the short-term efficacy and tolerability of atacicept in patients with relapsing-remitting MS. Patients enrolled in the study were randomized in a 1:1:1:1 manner to atacicept 25 mg, 75 mg, 150 mg, or placebo, administered as weekly subcutaneous injections after the initial escalation phase. The originally planned primary endpoint for the study was the change in mean number of gadolinium-enhancing lesions on T1 weighted MRI per patient, per scan, between weeks 12 and 36. Secondary endpoints were the mean number of gadolinium-enhancing T1 lesions per patient per scan from weeks 24 to 36; numbers of new T1 hypointense lesions per patient at weeks 12, 24, and 36; and the proportion of patients free from relapse. Tertiary endpoint was the annualized relapse rate.

The study was terminated early after an independent data and safety monitoring board noted an increased annualized relapse rate in the atacicept groups. The results reported are based on an intention-to-treat population of 255 patients with a median duration of 211 days in the double-blind phase. Of these 255 patients, 63 were randomized to the 25 mg group, 64 to the 75 mg group, 65 to the 150 mg group, and 63 to placebo. Ninety (35%) patients completed the originally planned 36 weeks, 26 (10%) discontinued before study termination due to lack of efficacy or other reasons, and 139 (55%) discontinued because of study termination. The annualized relapse rate was higher in the atacicept groups compared to placebo, with the difference being statistically significant for the 25 and 150 mg groups (0.38 for placebo, 0.86 for the 25 mg group, 0.79 for the 75 mg group, and 0.98 for the 150 mg group). The proportion of relapse-free patients was also higher in the placebo group compared to the atacicept groups (81% for placebo, 70% for the 25 mg, 72% for the 75 mg, and 62% for the 150 mg group). The mean number of gadolinium-enhancing lesions per patient per scan, which was the originally intended primary endpoint, did not differ between the treatment groups.

■ COMMENTARY

ATAMS was a Phase 2 trial of atacicept, a B-cell targeted therapy for relapsing MS, that was terminated early, as it appeared to have deleterious effects on relapses. Prior

data from clinical trials and real world experience, which demonstrated high efficacy of B-cell targeted therapies such as rituximab, led to the hypothesis that atacicept, which suppresses B cell function, would have a positive effect as well. The reasons for this negative clinical effect are being investigated and not known yet. While anti-CD 20 therapies like rituximab result in B-cell depletion with selective sparing of some progenitor B-cells and plasma cells, atacicept targets mature B-cells and plasma cells while sparing B-cell progenitors and memory cells. The differential influence of these therapies on B-cell sub-populations and the variable effects of the individual B-cell sub-populations on inflammation and regulation and repair might explain some of contrasting effects. The paradoxical and unexpected effect of atacicept highlights the limitations of our current understanding of the immune mechanisms involved in MS. A more comprehensive knowledge will help us develop better targets for intervention in the treatment of MS. ■

Non-Oculopharyngeal Involvement in OPMD

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: *Oculopharyngeal muscular dystrophy is a rare, autosomal dominant neuromuscular disorder that has recently been genetically defined and may be treatable with myoblast transplantation.*

Source: Witting N, et al. Ocular, bulbar, limb, and cardiopulmonary involvement in oculopharyngeal muscular dystrophy. *Acta Neurol Scand* 2014; Mar. 10. DOI: 10.1111/ane.12244 [Epub ahead of print].

Typically presenting in middle-age with ptosis, ophthalmoplegia, dysarthria, and dysphagia, oculopharyngeal muscular dystrophy (OPMD) is a slowly progressive, autosomal dominant genetic disorder that may also be associated with proximal and distal limb weakness. Linked to chromosome 14q11.2-q13, it results from a GCG trinucleotide repeat expansion of the polyadenylate (polyA) binding protein nuclear 1 gene (PABPN1), leading to an expanded polyalanine tract at the N-terminal of the PABPN1 protein. Genetic analysis now permits diagnosis of atypical cases, offering the opportunity to determine what, if any, extra-muscular involvement occurs.

Spearheaded by the Neuromuscular Research Unit, University of Copenhagen, Rigshospitalet, Copenhagen, Denmark, all 19 genetically verified OPMD patients in Denmark, encompassing 11 OPMD families, were invited to participate in this cross-sectional study. Due to logistic issues, five declined and one asymptomatic patient was excluded, leaving 13 patients from eight families to be studied. All patients underwent ophthalmologic evaluation, bulbar function testing including a timed swallow test (80 mL of 5° cold water in ≤ 7 seconds is normal), pulmonary function testing including forced expiratory vital (FEV1) capacity with a facial mask in all (due to facial weakness in some), and cardiac examination including electrocardiography (ECG), transthoracic echocardiography, and 48-hour Holter monitoring.

Among six male and seven female symptomatic OPMD patients, ptosis or limb weakness was the presenting sign in eight and five persons, respectively. All 13 had ptosis, with nine demonstrating ophthalmoplegia, and 11 had dysphagia, with the youngest two patients (41 and 47 years old), spared. Mean "swallow test" time was 34 seconds. Limb strength, both proximal and distal, declined with age, and was worse in legs than arms, but no proximal-distal gradient was found. None had cardiac symptoms or findings considered abnormal for age, while six patients, all older than age 60, had > 20% reduction in FEV1. Pulmonary, but not cardiac, involvement is seen in OPMD and is mild. Dysphagia, though the determinant of prognosis and the cause of poor nutrition and life-threatening aspiration pneumonia, is not a presenting complaint. Limb weakness, however, is common and may be the presenting complaint.

■ COMMENTARY

Although no specific treatment currently exists for OPMD, surgery may be offered to correct ptosis and dysphagia, and myoblast transplantation may become an option in the future. In a Phase 1/2a clinical study[1] using myoblasts harvested from unaffected quadriceps or sternocleidomastoid muscles, 12 OPMD patients underwent autologous transplantation, with a median of 178 million myoblasts injected into the constrictor muscles of the pharynx following cricopharyngeal myotomy. Over a 2-year period, no adverse effects were noted. Although limb weakness progressed during follow up, no deterioration of swallowing was seen in 10 patients, as measured by videoendoscopic swallowing study (VESS) and videofluoroscopy of swallowing (VFS). Upper esophageal sphincter function improved in six patients using VESS and in two using VFS, and swallowing time on the "swallow test" improved from 23.7 to 10.2 seconds (normal: ≤ 7 seconds). Improved quality of life (QOL), as measured by QOL questionnaires, was appreciated in all. Autologous myoblast transplantation appears safe and effective for OPMD and larger studies are warranted. ■

Reference

1. Perie S, et al. Autologous myoblast transplantation for oculopharyngeal muscular dystrophy: A Phase I/IIa clinical study. *Mol Ther* 2014;22:219-225.

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. Which of the following statements regarding hyperbaric oxygen therapy (HBO2T) and traumatic brain injury (TBI) is false?
a. Mild TBI is seen less frequently now on the battlefield.
b. Mild TBI is the signature injury of the United States global war on terrorism.
c. Soldiers who sustain blast-related postconcussion syndrome suffer headaches, dizziness, balance problems, and behavioral and cognitive dysfunction.
d. HBO2T has not been proven to be of benefit in patients with mild TBI and PCS.

2. Which of the following is true about mild cognitive impairment (MCI) in early Parkinson's disease?
a. MCI is associated with increased age.
b. MCI is more frequently seen in women rather than in men.
c. MCI does not correlate with motor dysfunction.
d. MCI is non-progressive.
e. MCI is measured equally well by the Modified Mini-Mental Status Examination and the Montreal Cognitive Assessment tests.

3. The so-called Z-drugs used for sleep (zolpidem, zopiclone, and zalephon) are not associated with increased mortality.
a. True
b. False

4. In the ATAMS (atacicept) study of multiple sclerosis, which of the following observations is true?
a. Patients in the placebo group had fewer relapses than those treated with atacicept.
b. More relapse-free patients were in the placebo group compared to the treated groups.
c. The study was terminated early because of higher relapse rates in the treated groups.
d. All of the above

5. Which statement regarding oculopharyngeal muscular dystrophy is false?
a. Forced expiratory vital capacity may be reduced.
b. 48-hour Holter monitoring is often abnormal.
c. Transthoracic echocardiography is usually normal.
d. Most patients have normal electrocardiography recordings.

6. Hemicraniectomy for treatment of large middle cerebral artery infarcts improves neurological recovery.
a. True
b. False

7. Rapid lowering of blood pressure in patients with intracerebral hemorrhage results in a worse neurological outcome.
a. True
b. False

In Future Issues:

Management of Brain Cavernous Malformations

Neurology Alert

2014 Reader Survey

In an effort ensure *Neurology Alert* is addressing the issues most important to you, we ask that you take a few minutes to complete and return this survey. *T*he results will be used to ensure you are getting the information.

Instructions: Mark your answers by filling in the appropriate bubbles. Please write your answers to the open-ended questions in the space provided. Either fax the completed questionnaire to 404-492-5933, or return it in the enclosed postage-paid envelope. The deadline is **July 1, 2014**.

In future issues of *Neurology Alert*, would you like to see more or less coverage of the following topics?

	A. more coverage	B. less coverage	C. about the same amount
1. epilepsy	O A	O B	O C
2. behavioral neurology	O A	O B	O C
3. movement disorders	O A	O B	O C
4. pain	O A	O B	O C
5. peripheral neurology	O A	O B	O C
6. stroke	O A	O B	O C
7. trauma	O A	O B	O C
8. basic neuroscience	O A	O B	O C
9. Alzheimer's disease	O A	O B	O C
10. Parkinson's disease	O A	O B	O C
11. multiple sclerosis	O A	O B	O C
12. pathophysiology	O A	O B	O C

13. What other topics would you like to see discussed in *Neurology Alert*? _____

_____

_____

14. Are the articles in *Neurology Alert* written about issues of importance and concern to you?

O A. always O B. most of the time O C. some of the time O D. rarely O E. never

15. Are the articles in *Neurology Alert*

O A. Too short O B. Too long O C. About right

16. What type of information not currently provided in *Neurology Alert* would you like to see added? _____

_____

_____

Please rate your level of satisfaction with the items listed.

	A. excellent	B. good	C. fair	D. poor
17. quality of newsletter	○ A	○ B	○ C	○ D
18. article selections	○ A	○ B	○ C	○ D
19. timeliness	○ A	○ B	○ C	○ D
20. quality of commentary	○ A	○ B	○ C	○ D
21. clearness of abstracts	○ A	○ B	○ C	○ D
22. overall value	○ A	○ B	○ C	○ D
23. customer service	○ A	○ B	○ C	○ D

24. To what other publications or information sources about neurology do you subscribe?

_____

_____

25. Including *Neurology Alert,* which publication or information source do you find most useful, and why?

_____

_____

26. Which website related to your position do you use most often?

_____

_____

27. Please list the top three challenges you face in your job today.

_____

_____

28. Please describe your work place:

○ A. private practice ○ B. hospital ○ C. government institution ○ D. research

○ E. Other _____

29. Has the information in *Neurology Alert* changed your clinical practice?

○ A. yes
○ B. no

If yes, how? _____

_____

Contact information _____

_____