AHC Media

Vol. 34, Issue 2, October 2014
www.ahcmedia.com

Neurology [ALERT®]

Evidence-based summaries of the latest clinical neurology research

ABSTRACT & COMMENTARY

Is it Possible to Have Idiopathic Epilepsy Without Seizures?

By Douglas Labar, MD, PhD

Professor of Neurology, Weill Cornell Medical College

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

SYNOPSIS: In a functional MRI study, it appears that healthy siblings of patients with juvenile myoclonic epilepsy have hyper-connectivity between motor brain regions that may result in hyper-excitable responses.

SOURCE: Wandschneider B, et al. Motor co-activation in siblings of patients with juvenile myoclonic epilepsy: An imaging endophenotype? *Brain* 2014;137:2469-2479.

While a history of recurrent seizures is obligate for the diagnosis of idiopathic generalized epilepsies (IGE), one may now wonder whether seizures are only the tip of the iceberg of atypical brain functional organizational features in these syndromes, for which a polygenetic underlying etiology seems likely.

Functional magnetic resonance imaging (fMRI) has recently revealed a pattern of motor cortex activation with a working memory paradigm that differs significantly between normal subjects and unaffected siblings of patients with juvenile myoclonic epilepsy (JME), a sub-type of IGE.[1] Study participants were asked to move a joystick to a randomly presented baseline dot position on a computer screen ("0-back" condition) or, to test working memory, either move the joystick to the immediately prior presented dot position ("1-back" condition) or to the position before that ("2-back" condition). fMRI activity with the "0-back" baseline task was subtracted from the "1-back" or "2-back" task activities, thus isolating the fMRI changes associated with the working memory components of the later tasks. Because all the tasks required hand movements of the joystick, motor cortex activation was always seen in all test conditions in normal

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.

Weill Cornell Medical College

NewYork-Presbyterian

Neurology
[ALERT]

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

SUBSCRIBER INFORMATION
1-800-688-2421
customerservice@ahcmedia.com
www.ahcmedia.com

Editorial E-Mail:
leslie.coplin@ahcmedia.com

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

Subscription Prices
United States:
Print: 1 year with free *AMA PRA Category 1 Credits™*: $369
Add $19.99 for shipping & handling.
Online only: 1 year (Single user) with ***free*** *AMA PRA Category 1 Credits™*: $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.
Back issues: Missing issues will be fulfilled by customer service free of charge when contacted within one month of the missing issue's date.

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 only claim 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

subjects and JME siblings. On both working memory tasks (compared with the baseline task), prefrontal and parietal areas were activated similarly in normal subjects and JME siblings. However, with the "1-back" memory test, the normal subjects deactivated primary motor cortex more than the JME siblings, and with the "2-back" memory task, the normal subjects deactivated primary motor and supplementary motor cortices more than the JME siblings. Stated differently, when deploying working memory, the JME siblings failed to deactivate primary and supplementary motor areas in the expected manner. Similar findings had previously been seen in JME patients.[2] The authors propose that abnormal hyper-connectivity between prefrontal cognitive and motor system cortical areas may contribute to the occurrence of cognitively triggered myoclonic jerks in JME patients.

■ COMMENTARY

Several other studies also have demonstrated a variety of unique ways in which unaffected siblings of patients with IGE differ from normal subjects. In the IGE siblings, these include: 1) increased motor cortex excitability as demonstrated by transcranial magnetic stimulation (TMS),[3] 2) deficient nonverbal reasoning, attention, and working memory,[4] and 3) presence of electroencephalographic (EEG) spikes (in 17%) and high amplitude somatosensory evoked potentials (in 21%).[5] Some authors have suggested that these findings may be considered endophenotypes of IGE.

Endophenotypes are intermediate conditions more common in family members of ill patients than in the general population. Such endophenotypes are biological phenotypes which, while often requiring extra targeted testing to be demonstrated, may be closer to the genotypes than the more severe clinical epilepsy syndromes. Identification of endophenotypes thus may contribute significantly to the identification of underlying susceptibility genes. Finally, more and better characterization of IGE endophenotypes may influence our overall concepts concerning these illnesses. While we would never diagnose an unaffected IGE sibling who has abnormal fMRI motor cortex connectivity, TMS cortical motor hyper-excitability, working memory deficits, or EEG spikes as having "IGE without seizures," it would be hard to dispute that such a clinical-epilepsy-unaffected IGE sibling does have some degree of atypical brain functional organization attributable to susceptibility genes shared with the their clinical-epilepsy-affected sibling. ■

REFERENCES

1. Wandschneider B, et al. Motor co-activation in siblings of patients with juvenile myoclonic epilepsy: An imaging endophenotype? *Brain* 2014;137:2469-2479.
2. Vollmar C, et al. Motor system hyper-connectivity in juvenile myoclonic epilepsy: A cognitive functional magnetic resonance imaging study. *Brain* 2011;134:1710-1719.
3. Badawy R, et al. Capturing the epileptic trait: Cortical excitability measures in patients and their unaffected siblings. *Brain* 2013;136(Pt 4):1177-1191.
4. Chowdhury F, et al. Impaired cognitive function in idiopathic generalized epilepsy and unaffected family members: An epilepsy phenotype. *Epilepsia* 2014;55:835-840.
5. Atakli D, et al. Somatosensory evoked potentials and EEG findings in siblings of juvenile myoclonic epilepsy patients. *Epileptic Disord* 1999;1:173-177.

ABSTRACT & COMMENTARY

How Best to Do the 'Jolly' Test

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 the electrophysiological evaluation of patients with myasthenic syndromes, adding 1 minute of exercise is the most sensitive method of eliciting a significant decremental response.

SOURCE: Oh SJ, et al. One-minute exercise is best for evaluation of postexercise exhaustion in myasthenia gravis. *Muscle Nerve* 2014;50:413-416.

Friedrich Jolly (1844-1904), German neurologist and psychiatrist, student of Georg Meissner (Meissner's corpuscles), and pioneer of myasthenia research, described the electrophysiological aspects of myasthenic fatigue, which form the basis of the repetitive nerve stimulation (RNS) test that bears his name. An abnormal "Jolly" test is a reproducible decrement of muscle amplitude of > 10% during 3 Hz repetitive stimulation, and results from a decreased safety margin, due to abnormal acetylcholine (Ach) receptors, and consequent failure to reach threshold depolarization with progressively fewer muscle fibers depolarizing as nerve terminals become partially depleted of ACh. Exercise exacerbates this decrement, known as postexercise exhaustion (PEE), but the best exercise duration to achieve PEE is debatable, and is the subject of this study.

Among 45 myasthenia gravis (MG) patients who consented to this study, 32 patients (17 men and 15 women, with a mean age of 54.6 years) had an abnormal decremental response on Jolly testing either at rest or postexercise. MG diagnosis was based on positive testing of any of acetylcholine receptor antibodies (n = 24), muscle-specific kinase antibodies (1 of 8 seronegative patients), RNS, or single-fiber electromyography (positive in all 16 who underwent testing).

To determine the exercise duration that would elicit maximum decrement, RNS on the abductor digiti quinti (ADQ) muscle was performed using supra-maximal stimulation at 3 Hz for 2 seconds, under standard technique, immediately following exercise lasting 10, 30, and 60 seconds, as well as 30, 60, 120, 180, and 240 seconds postexercise. Exercise of the ADQ was performed by having the subjects spread their fingers against maximal resistance from the examiner. Anticholinesterase medications were held for at least 12 hours prior to RNS, skin temperature was kept at or above 32° C, peak-to-peak amplitude was used for measurements, and decrement was measured by comparing the smallest response to the initial response. Statistical analysis comprised the paired t-test or chi-square test, with $P < 0.05$ considered statistically significant.

At rest, the mean decrement was 16% among all 32 patients, with an abnormal decrement observed at rest in 21 (66%), and in 11 patients only postexercise. Decrement was significantly increased at 2 and 3 minutes following 30 seconds of exercise, and at 2, 3, and 4 minutes following 60 seconds of exercise. Significantly, in 11 patients who only demonstrated decrement after exercise but not at rest, it was observed in 8 of 11 after 60 seconds of exercise, but in only 5 of 11 after 30 seconds of exercise. Postexercise decrement in myasthenia is best elicited by performing RNS after 1 minute of exercise.

■ COMMENTARY

A non-progressive, or U-shaped, pattern of decrement to 3 Hz RNS is characteristic of MG. How does this compare to Lambert-Eaton myasthenic syndrome (LEMS)? To address this question, retrospective review was undertaken of RNS studies performed on 58 muscles in 34 LEMS patients and on 54 muscles in 44 MG patients. Calculations were made of the "early decrement" (percent fall in peak motor amplitude from the first to the fourth or fifth response), and the "late decrement" (percent fall of first to the ninth or tenth response), and the ratio between the early and late decrement was calculated as well ("Late/Early"). Despite overlap in individual cases, late decrement was greater than early decrement in LEMS, with the reverse true in MG, indicating that when the decrement becomes progressively greater during 3 Hz-RNS, the diagnosis is more likely to be LEMS rather than MG.[1] ■

REFERENCE

1. Sanders D, et al. Is the decremental pattern in Lambert-Eaton myasthenic syndrome different from that in myasthenia gravis? *Neurology* 2014;82(Suppl P2):80.

ABSTRACT & COMMENTARY

Brain Natriuretic Peptide – A Biomarker for Cognitive Decline?

By Richard S. Isaacson, MD

Associate Professor of Neurology (Education), Weill Cornell Medical College

Dr. Isaacson reports he is a retained consultant and on the speakers bureau for Novartis, and is a retained consultant for and receives grant/research support from Accera.

SYNOPSIS: A new study has found an association between pro-brain natriuretic peptide (NT-proBNP) and cognitive decline in older adults at high risk of cardiovascular disease.

SOURCES: Wijsman LW, et al. N-terminal pro-brain natriuretic peptide and cognitive decline in older adults at high cardiovascular risk. *Ann Neurol* 2014;76:213-222. Caplan LR. Cognitive decline and brain natriuretic peptide: How are they related? *Ann Neurol* 2014;76:165-166.

While there are many uncertainties as to the predictors of cognitive decline, as well as uncertainty regarding the exact causes of vascular and other neurodegenerative dementias that are common with advancing age, new research has attempted to further our understanding of the myriad of potential risk factors. A prospective cohort study by Wijsman and colleagues (Leiden University Medical Center, The Netherlands) recently found that subjects with higher levels of a metabolite of brain natriuretic peptide (BNP) called N-terminal pro-BNP (NT-proBNP) had worse cognitive function and steeper cognitive decline (mean age = 75) over a mean follow-up of 3.2 years. Several cognitive domains were affected and these associations were found to be independent of cardiovascular disease and risk factors in more than 5000 participants of the PROspective Study of Pravastatin in the Elderly at Risk.

Although prior studies have also found an association of these peptides with brain function, most have focused on how NT-proBNP relates to several cardiac diagnoses. Additionally, this is the first study reporting on the association of NT-proBNP and cognitive function and decline, using a much more comprehensive, standardized cognitive test battery over several years. While it is difficult to speculate as to the reason for such an association, and further studies are warranted, these cardiovascular diseases are intimately linked to cognitive dysfunction and dementia. In the cardiovascular literature, patients who have been found to have elevated levels of either BNP or NT-proBNP have a higher risk of morbidity and mortality from heart failure, and these biomarkers may also be elevated in those with atrial fibrillation, myocardial infarction, and renal failure. Further, NT-proBNP has been used clinically to help screen for those likely to develop atrial fibrillation and lower the threshold for prolonged cardiac rhythm monitoring.

In the accompanying editorial by Dr. Louis Caplan (Beth Israel Deaconess Medical Center, Harvard Medical School), several hypotheses are discussed about potential relationships that then can be further studied to determine the pathophysiologic underpinnings of this association. For example, since elevated NT-proBNP is a recognized marker for atrial fibrillation, cognitive decline could potentially be explained by embolic infarcts over time, negatively affecting cortical function. Chronic cerebrovascular disease and associated white matter disease (although this was not specifically evaluated in this study) may be related to decline in several cognitive domains, while also contributing to mixed vascular-Alzheimer pathology (a commonly encountered condition in clinical practice). Since elevated NT-proBNP levels may be found in congestive heart failure, another potential cause could be cognitive manifestations known in the literature as "cardiac encephalopathy" (characterized by abnormalities in executive function, as well as abulia).

At this time, from a practical clinical perspective, alterations in clinical practice by ordering NT-proBNP to help stratify patients cannot yet clearly be recommended. However, these data continue to expand upon great progress over the last decade in determining modifiable, as well as non-modifiable risk factors, involved in the development of cognitive decline and dementia.[1] ■

REFERENCE

1. Oboudiyat C, et al. Alzheimer's disease. *Semin Neurol* 2013;33:313-329.

ABSTRACT & COMMENTARY

Therapeutic Target for DBS for Dystonia

By Alexander Shtilbans, MD, PhD

Assistant Professor of Neurology, Weil Cornell Medical College

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

SYNOPSIS: The authors of the current study created a volume-of-tissue-activation model in order to identify the area within the globus pallidus that provides the most effective target for deep brain stimulation for dystonia.

SOURCE: Cheung T, et al. Defining a therapeutic target for pallidal deep brain stimulation for dystonia. *Ann Neurol* 2014;76:22-30.

Dystonia is a movement disorder characterized by abnormal muscle contraction and abnormal postures. The pharmacological treatment consists mostly of anticholinergic and antispasticity agents that have systemic side effects. Focal dystonia can be effectively treated with botulinum toxin injections. Severe generalized dystonia, refractory to medications, can be effectively treated surgically with deep brain stimulation (DBS) of the globus pallidus pars interna (GPi). DBS is also used for treatment of Parkinson disease and essential tremor, although different anatomical targets are used. Although the exact mechanism of action of DBS is unknown, it is believed to inhibit electrochemical conduction through myelinated nerve fibers of the motor

control regions, alleviating the dystonic symptoms. The outcome of this surgical treatment varies depending on the position of the electrodes in the GPi and the stimulation parameters used. Furthermore, the effect of the stimulation on dystonia might be delayed by 3 to 5 months after the surgery, for unclear reasons. Therefore, it is vitally important to ensure proper placement of the electrodes within GPi to maximize the effect. For this reason, models studying volume-of-tissue-activation (VTA), which can predict effective regions of stimulation, have been developed previously for Parkinson disease.

The objective of this study by Cheung et al was to identify and characterize the region of the brain that was targeted in clinically successful pallidal stimulation for dystonia, utilizing VTA models. The authors retrospectively studied a cohort of 21 primary DYT1 dystonia patients, treated for at least 1 year with bilateral DBS in GPi. Upon placement of the electrodes, the 12-month stimulation parameters were entered into the model to calculate individualized VTA. Clinically, changes in disease severity were measured in patients using Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS). The authors associated each VTA with its corresponding BFMDRS score. The authors constructed target volume using clinical improvement and activation thresholds of 75%. As a result, the mean improvement in the 12-month period was calculated to be 83%. The mean individual VTA volume was 501 mm^3. The authors then created a dystonia stimulation atlas (DSA) for the studied cohort of patients using stereotactic mapping. The analysis revealed that 32 of the 42 electrodes evaluated met the 75% improvement threshold. Using this threshold, the volume of the calculated target within GPi was 152.7 mm^3.

The authors concluded that the resulting maps provided quantified localization of the regions that underwent direct activation after 12 months of follow-up. Considering the stimulation areas that were in common, there was a relatively small area located in the middle of GPi representing the best potential target for therapeutic DBS for dystonia. Therefore, the atlas might be a useful tool for physicians implanting and programming the stimulation devices. The authors further suggested that increasing total electrical energy delivered to the tissue to achieve better clinical improvement may not provide the desired effect, whereas simulation of the correct regions within GPi should provide a better outcome.

■ COMMENTARY

The authors of the current study created a model to identify the area within GPi that might provide the most effective target for DBS, resulting in the best possible clinical improvement of dystonia symptoms. The authors correctly acknowledged limitations of this study, which included individual patient variability and limitations of MRI resolution, possibly affecting the accuracy of anatomic mapping. In addition, this cohort of patients showed better outcomes in comparison to previously reported groups of patients with dystonia treated with DBS. The clinical evaluations were performed in an open-label fashion, which potentially could have played a role in the better-than-average outcomes.

The study examines only patients with DYT1 dystonia, and it would be interesting to see if the proposed model also applies to other types of generalized dystonia. Furthermore, since the onset of the clinical improvement after DBS for dystonia can be delayed up to several months, it would be useful to know if the onset of improvement correlates with the location of the electrodes within GPi according to the described model in this study.

The authors rightfully argue that the region they identified represents a potential target and can help with surgical planning. Current research in DBS technology involves programmable selection of lateral directional stimulation to achieve better clinical results. The described model could potentially help guide a clinician in choosing the appropriate direction for stimulation. Therefore, these targets are important and warrant further investigation through validation studies in larger and more diverse groups of patients with dystonia. ■

ABSTRACT & COMMENTARY

Targeting Calcitonin Gene-Related Peptide in Attempts to Prevent Migraine Headaches

By Dara Jamieson, MD

Assistant Professor of Clinical Neurology, Weill Cornell Medical College

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

SYNOPSIS: Blockade of the vasoactive peptide calcitonin gene-related peptide, using monoclonal antibodies or small orally absorbed molecules, may decrease the disability of episodic migraine. However, safety concerns with these agents remain an issue.

SOURCES: Dodick DW, et al. Safety and efficacy of LY2951742, a monoclonal antibody to calcitonin gene-related peptide, for the prevention of migraine: A phase 2, randomised, double-blind, placebo-controlled study. *Lancet Neurol* 2014;13:885-892.
Ho TW, et al. Randomized controlled trial of the CGRP receptor antagonist telcagepant for migraine prevention. *Neurology* 2014;83:958-966.

Patients with migraine headaches that are frequent, disabling, or refractory to acute treatment should be offered a treatment to decrease the frequency and severity. However, there are few effective preventive medications available. New migraine-specific targets, such as calcitonin gene-related peptide (CGRP), are being investigated to improve preventive efficacy. This study from Dodick et al assessed the efficacy and safety of LY2951742, a fully humanised monoclonal antibody to CGRP, in migraine prevention in men and women, aged 18-65 years, with at least a 1-year history of migraine, according to the International Classification of Headache Disorders (ICHD-II). The migraineurs had between four and 14 migraine headache days per month, which is defined as frequent episodic migraine, but the patients did not have chronic migraine. In a Phase 2 proof-of-concept study performed at 35 centers in the United States, patients who were not on any preventive medication were randomized to LY2951742 (150 mg) or placebo. LY2951742 (n = 108) or placebo (n = 110) was injected subcutaneously by masked trained site personnel once every 2 weeks for 12 weeks. Primary endpoint responders were defined as patients who had a > 50% reduction in the number of migraine headache days in a 28-day period. Safety was assessed over 24 weeks, including the 12-week treatment period and the subsequent 12 weeks after study drug administration. Efficacy analyses were performed by an intention-to-treat, mixed-effects model of repeated measures. Safety measures were analyzed according to the treatment received. The mean change from baseline to week 12 in the number of migraine headache days was -4.2 (SD = 3.1; 62.5% decrease) in the LY2951742 group compared with -3.0 (SD = 3.0; 42.3% decrease) in the placebo group (least-squares mean difference -1.2, 90% CI -1.9 to -0.6; $P = 0.0030$). Adverse events that occurred more frequently with LY2951742 than with placebo included injection site pain, erythema, or both (21 [20%] of 107 vs 7 [6%] of 110), upper respiratory tract infections (18 [17%] vs 10 [9%]), and abdominal pain (6 [6%] vs 3 [3%]). None of the rare serious adverse events was deemed to be related to the study drug. There were no clinically important changes in laboratory parameters, ECGs, or vital signs between the groups. LY2951742, a well-tolerated parenteral preventive medication, was better than placebo for all secondary efficacy endpoints: monthly migraine attacks, migraine headache days and probable migraine headache days, total headache days, and responder rate. These encouraging results provide preliminary evidence that LY2951742 might be beneficial in migraine prevention and provide support for the role of CGRP in the pathogenesis of migraine.

The study of Ho et al evaluated whether the CGRP receptor-antagonist telcagepant was effective for migraine prevention. In this randomized, double-blind, placebo-controlled, multicenter trial, patients with episodic migraine were randomized to oral telcagepant 140 mg, telcagepant 280 mg, or placebo twice daily for 12 weeks. There was evidence that telcagepant resulted in a larger reduction from baseline than did placebo for mean-monthly headache days and migraine/probable headache days. However, 13 patients receiving telcagepant, but none on placebo, developed aminotransferase elevations more than threefold above normal; therefore, the trial was prematurely terminated. Of the 13 patients with liver enzyme elevation, 2 were symptomatic and had > 10-fold elevations above normal, with resolution after treatment was discontinued. The originally planned efficacy analysis over 12 weeks was not performed due to limited data at later time points.

■ COMMENTARY

The mechanisms of action of most migraine-preventive medications are poorly understood and these medications may not directly impact known migraine pathophysiology. This lack of specific targeted therapy is reflected in patients' lack of satisfaction with the currently available medications used to decrease the frequency and severity of migraine attacks. Specific, targeted preventive therapies are needed. Multiple vasoactive peptides that promote vasodilation and neuroinflammation are involved in the pathogenesis of migraine. Antagonists to specific vasoactive peptides, such as CGRP, have been investigated with variable results. Since CGRP plays an important role in the pathogenesis of migraine, it is an appropriate target for both acute and preventive treatment. Small-molecule CGRP receptor antagonists have shown efficacy in Phase 2 and Phase 3 trials for acute abortive treatment of migraine; however, hepatotoxicity, noted with investigation of CGRP receptor antagonists for preventive treatment, has slowed further research. Telcagepant is no longer under investigation for acute or preventive treatment of migraine. However, new small-molecule CGRP receptor antagonists may hold future promise for the acute treatment of migraine. Because monoclonal antibodies against CGRP and its receptor have long half-lives, they are appropriate for preventive therapy. The large molecules of the monoclonal antibodies are not degraded in the liver, decreasing the potential for drug-drug interactions and hepatotoxicity, as has been found with the small molecules of the CGRP antagonists. In this study of LY2951742, monoclonal antibodies that block the activity of CGRP decreased the disability of episodic

Continued on page 16

Neurology [ALERT]

Stroke Alert

By Matthew E. Fink, MD

Dehydration Is a Poor Prognostic Sign in Acute Ischemic Stroke Patients

SOURCE: Liu CH, et al. Dehydration is an independent predictor of discharge outcome and admission cost in acute ischaemic stroke. *Europ J Neurol* 2014;21:1184-1191.

Several factors have been reported to predict the outcome of acute stroke, including the modified Rankin scale, length of hospital stay, age and gender, severity of presenting deficit as measured by the initial NIH Stroke Scale, history of diabetes, and in-hospital infections. Dehydration status upon admission has been a controversial prognostic indicator, and a group of investigators from Taiwan, led by Liu et al, have evaluated the importance of dehydration on admission in stroke patients admitted between January 2009 and December 2011. In total, they examined the records of 2570 acute ischemic stroke patients and 573 acute hemorrhagic stroke patients. They divided the group into those deemed dehydrated, based on a BUN/creatinine ratio ≥ 15, vs non-dehydrated, with a ratio < 15. Patients with confounding illnesses, such as congestive heart failure, renal insufficiency, liver cirrhosis, and vascular abnormalities, were excluded from this study. They also examined demographics, hospital admission costs, and discharge outcomes using the modified Rankin scale and the Barthel index.

In a multivariate analysis using logistic and linear regression, investigators found that acute ischemic stroke patients with admission dehydration had significantly higher rates of infection, worse discharge Barthel Index, worse discharge modified Rankin scale, and higher admission costs compared to those without dehydration. However, acute hemorrhagic stroke, with or without admission dehydration, showed no difference in discharge clinical outcomes or costs of hospitalization.

One of the confounding factors that was evaluated was the risk of venous thromboembolism, which is also associated with dehydration. It is notable that Chinese patients have a much lower risk of thromboembolism than do white or black patients, and this did not seem to play a significant role in the study. Dehydration is known to increase blood viscosity, reduce cardiac output, reduce blood pressure, and impair cerebral blood flow and collateral circulation to the brain. Although these mechanisms may have played a role in this evaluation, cerebral blood perfusion studies were not performed, and therefore these mechanisms were suggested, but not proven. On a clinical note, the above findings emphasize the importance of rapid correction of admission dehydration, with intravenous fluid replacement therapy as quickly as it can be safely administered. ■

Sodium Intake, Blood Pressure, and CVD – What Is a Neurologist To Advise?

SOURCE: Oparil S. Low sodium intake — cardiovascular health benefit or risk? *New Engl J Med* 2014;37:677-679.

In the August 14, 2014, issue of the *New England Journal of Medicine*, three research articles were published addressing the issues of sodium in the diet and its impact on blood pressure and cardiovascular consequences. This is a controversial area and resulted in the Institute of Medicine convening an expert committee to evaluate the evidence for a relationship between sodium intake and health outcomes. The committee concluded that although there was a positive relation between high sodium intake and the risk of cardiovascular disease, results from studies were insufficient to conclude whether a low sodium intake (less than 1.5 g per day) was associated with an increased or reduced risk of cardiovascular disease in the general population. The editorial by Suzanne Oparil, which references the other three articles in the same issue of the journal, reviews the existing evidence, and comes to the conclusion that it is still unclear whether a low sodium diet should be recommended as part of long-term prevention of cardiovascular disease. High sodium intake seems to be associated with elevations in blood pressure and increased cardiovascular events, including stroke, but what is considered to be a moderate range of sodium intake, defined as 3-6 g per day of sodium, may not have any negative effects on overall health. It is just not known. In addition, it appears that increasing the amount of potassium in the diet may have beneficial effects that are separate and independent of the consequences of high or low sodium.

We urge neurologists who are caring for patients at risk for stroke or who have already had a stroke to pay attention to both diet as well as blood pressure treatments, since hypertension continues to be the single most powerful modifiable risk factor for all stroke subtypes. Recommendations regarding optimal diet are uncertain at the present time, and we will need more research-based evidence before we can make recommendations regarding sodium, carbohydrate, or fat intake, as it relates to cardiovascular risk. ■

Continued from page 14

migraine, without any significant adverse events, other than the minor discomfort of a subcutaneous injection. The encouraging results of this Phase 2 study indicate long-term efficacy and safety of monoclonal antibodies directed against CGRP or its receptor. Further controlled studies are needed to assess the safety and efficacy of monoclonal CGRP antibodies for the prevention of migraine headaches and their related disability. ■

CME INSTRUCTIONS

To earn credit for this activity, please follow these instructions:
1. Read and study the activity, using the provided references for further research.
2. Scan the QR code to the right or log on to **www.cmecity.com** to take a post-test. 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 test, 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. **Some of the generalized epilepsies have a genetic basis and family members should be queried and evaluated.**
   a. True
   b. False

2. **Which of the following is correct regarding postexercise decrement in myasthenia?**
   a. Postexercise decrement in myasthenia is best elicited by performing repetitive nerve stimulation after 1 minute of exercise.
   b. Postexercise decrement in myasthenia is best elicited by performing repetitive nerve stimulation after 2 minutes of exercise.
   c. Postexercise decrement in myasthenia is best elicited by performing repetitive nerve stimulation after 3 minutes of exercise.
   d. Postexercise decrement in myasthenia is best elicited by performing repetitive nerve stimulation after 4 minutes of exercise.

3. **NT-proBNP has been found to be associated with a variety of cardiovascular and neurological conditions. All of the following have been found to have a potential association with the NT-proBNP biomarker *except*:**
   a. atrial fibrillation.
   b. cognitive decline.
   c. congestive heart failure.
   d. SIADH syndrome.
   e. myocardial infarction.

4. **Which of the following statements is *false* regarding deep brain stimulation (DBS) for movement disorders?**
   a. DBS has been demonstrated to be effective treatment for some patients with Parkinson disease.
   b. DBS has been demonstrated to be effective for treatment of some patients with dystonia.
   c. DBS has been demonstrated to be effective for treatment of some patients with tremor related to multiple sclerosis.
   d. The best target and stimulation parameters for DBS treatment of dystonia are still uncertain.

5. **Antagonists to CGRP have been associated with which of the following?**
   a. Hepatotoxicity
   b. Renal toxicity
   c. Increased bleeding
   d. Increased headaches
   e. Hair loss

6. **Dehydration is a risk for poor outcome after ischemic stroke and should be prevented.**
   a. True
   b. False

7. **Low sodium diet has been proven to reduce cardiovascular events, including stroke.**
   a. True
   b. False

[IN FUTURE ISSUES]

Prion Diseases