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INSIDE

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Does Therapeutic Hypothermia Affect Predictive Value of Somatosensory Evoked Potentials after CPR?

ABSTRACT & COMMENTARY

By Elayna Rubens, MD

Dr. Rubens is Assistant Professor of Neurology at Weill Cornell Medical College

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

Synopsis: *Bilateral absence of N20 responses in the setting of therapeutic hypothermia does not preclude neurologic recovery in comatose survivors of cardiac arrest.*

Source: Leithner C, et al. Does hypothermia influence the predictive value of bilateral absent N20 after cardiac arrest? *Neurology* 2010;74:965-969.

PREDICTING NEUROLOGIC RECOVERY IN COMATOSE SURVIVORS OF CARDIAC ARREST is a challenge faced routinely by neurologists in the inpatient setting. To date, therapeutic hypothermia (TH), where the patient's core temperature is maintained at 32-34 °C for 12-24 hours following resuscitation, is the only treatment modality that has been shown to improve neurologic outcome in this population. Because the currently accepted prognostic indicators of outcome after cardiac arrest were validated (and subsequently outlined in the 2006 AAN practice parameter) prior to the widespread use of TH, the accuracy of these indicators in patients treated with hypothermia is not yet clear. Of the established predictors, bilateral absence of the cortical N20 response in median nerve somatosensory evoked potential (SSEP) testing is considered to be the most reliable early indicator of a poor neurologic outcome and, in one small study, appeared equally useful in the setting of hypothermia. Prompted by a case of a patient who had a favorable neurologic recovery after TH despite an initially absent N20 bilaterally, Leithner and colleagues set out to examine the predictive value of bilateral absent N20 in the setting of therapeutic hypothermia.

In this study, the authors retrospectively analyzed the records of 185 consecutive patients treated with hypothermia following cardiac arrest. Of 185 patients, 112 had SSEP testing. Testing was performed more than 24 hours after resuscitation using a standard technique. The N20 responses were cat-

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egorized as: absent, pathologic (prolonged latency and/or reduced amplitude of the cortical response), or normal. Using a clinical database, baseline and follow up information regarding neurologic outcome was obtained. Outcomes were determined at the time of the ICU discharge and assessed using the Pittsburgh cerebral performance category (CPC).

The findings revealed that N20 was absent in 36 (32%) patients, pathologic in 22 (20%) patients, and normal in 54 (48%) patients. Of the 36 patients with bilaterally absent N20 responses, 35 (97%) had poor outcome (CPC 4 or 5). One patient with initially absent N20 response three days after cardiac arrest (after normothermia) had an excellent outcome (CPC1) with subsequent recovery of the N20 response at 18 month follow up testing. In this patient, the peripheral (N9) and cervical (N13) responses were significantly delayed on both initial and follow up testing. Though the peripheral response delay alone is unlikely to explain the initial absence of the cortical response, it does indicate a coexisting peripheral abnormality, which the authors suggest was due to alcoholic polyneuropathy and reduced extremity temperature at the time of the initial testing. The authors also identified another case in which the cortical response amplitudes were severely diminished such that the N20 was nearly absent three days after resuscitation (during normothermia). This patient also had a favorable outcome (CPC1) and recovery of normal N20 response amplitude nine days after cardiac arrest.

The authors conclude that their results reaffirm the high negative predictive value of bilaterally absent N20 responses in comatose survivors of cardiac arrest in the setting of TH. However, the identification of two cases of absent, or nearly absent, N20 responses after cardiac arrest treated with hypothermia with subsequent recovery of both neurologic functioning and cortical somatosensory evoked responses suggests that the certainty of this prediction may be diminished in patients treated with hypothermia. The authors propose that hypothermia may allow for a delayed functional recovery of somatosensory evoked responses well beyond the established one to three day period post resuscitation during which the test is typically performed.

■ COMMENTARY

This study highlights the importance of rigorous re-evaluation of the standard indicators of neurologic prognosis following cardiopulmonary resuscitation in patients undergoing therapeutic hypothermia. Inherent in hypothermia treatment is the use of sedative and paralytic agents which hinder clinical assessment and therefore increase dependence on neurophysiologic parameters, particularly SSEP. Though this is a small study with a bias towards identification of false positive results, it suggests that absent N20 may not be as reliable early in the course of TH and that meaningful recovery of cortical responses may occur later than previously expected in these patients. Further prospective studies designed to establish false positive rates and appropriate timing of evoked potential testing are needed to guide decision making in patients treated with induced hypothermia. Until then, bilateral absence of the N20 response in these patients should be interpreted cautiously. ■

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Exercise and Parkinson's Disease

ABSTRACT & COMMENTARY

By Panida Piboolnurak, MD

Assistant Professor, Department of Neurology and Neuroscience, Weill Cornell Medical College

Dr. Piboolnurak reports no financial relationship relevant to this field of study.

Synopsis: *Exercise is beneficial for frontal lobe based executive functions. Although this study did not show benefit of exercise on mood and quality of life, this could be due to a floor effect of data.*

Source: Cruise KE, et al. Exercise and Parkinson's: Benefits for cognition and quality of life. *Acta Neurol Scand* 2010; March 1 (Epub ahead of print).

Depression and cognitive impairment are important predictors of the quality of life of patients with Parkinson's disease (PD). There is evidence suggesting benefit of exercise on mood disturbances and cognitive function, particularly on executive function. This study investigated the benefit of an exercise protocol on executive function and mood.

Patients with mild to moderate PD without significant cognitive impairment (MMSE < 24) were recruited. Patients with other neurological disorders, musculoskeletal diseases, or cardiovascular diseases that could inhibit them from exercise were excluded. Authors also excluded patients who had participated in regular resistance training in the previous 12 months. Thirty-five participants were selected and were allocated to either an immediate exercise program or delayed exercise group (control). Exercise program included resistance and aerobic exercises. Global cognitive function was assessed using MMSE and Australian National Adult Reading Test (AUSNART). Assessments specific to frontal (verbal fluency, spatial working memory and Stocking of Cambridge), fronto-temporal (spatial recognition memory), and temporal lobe (pattern recognition memory and semantic fluency) function were also obtained. Geriatric Depression Scale (GDS) was used for depression assessment. The Parkinson's Disease Questionnaire (PDQ-39) was used to evaluate the benefit of exercise on quality of life.

Exercise was shown to have a selective benefit for frontal lobe based executive function, but it did not show benefit on mood or quality of life. The authors explained that because 71% of participants were classified within the normal range for depression (GDS 0–4) and only two participants had very poor quality of life, exercise might not improve these areas beyond the normal range (floor effect). They also discussed that this study was limited by sampling bias because participants were recruited from PD support groups which likely involved people who are quite active at disease management. They suggested that this limitation be addressed by larger sample size and by recruiting participants from a clinic setting. Moreover, specifically screening participants for depression as an inclusion criterion would allow for more in depth assessment of the benefit of exercise on mood.

■ COMMENTARY

Many studies have suggested that exercise is beneficial for patients with Parkinson's disease. The benefit of exercise is not only for physical function, but also for cognition and mood. Although the mechanism of these effects are unknown, the animal studies using the MPTP model have shown that exercise improves motor function, enhances neuroplasticity in the basal ganglia and increases neurotrophic factors. Given current evidence, regular resistance and aerobic exercises should be recommended to patients with Parkinson's Disease. ■

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) in children

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 children, CIDP is less common than in adults, but has a better long-tern prognosis.*

Source: Jo HY, et al. Chronic inflammatory demyelinating polyradiculoneuropathy in children: Characterized by subacute, predominantly motor dominant polyneuropathy with a favorable response to the treatment. *Acta Neurol Scand* 2010:121: 342–347 DOI: 10.1111/j.1600-0404.2009.01222.x.

With an estimated prevalence of approximately 0.5/100,000, compared to 1-2/100,000 in adults, childhood chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is rare and remains poorly understood. To further our appreciation of this disease, retrospective record review was undertaken of all CIDP patients seen in Pusan National University Hospital, Yangsan City, South Korea, between 1996-2008, and divided into childhood (age < 16 years) and adult cases. Clinical diagnostic criteria comprised more than four weeks of progressive weakness or sensory impairment with hyporeflexia, or a relapsing course of same, lasting beyond 12 months. Laboratory investigations included routine blood studies, cerebrospinal fluid analysis, and electrodiagnostic testing, with criteria for CIDP being those established by the European Neuromuscular Center International Workshop (Neuromusc Disord 2002;12:195–200). Patients with HIV or other infections, monoclonal gammopathy, malignancy, or specific anti-ganglioside antibodies were excluded. All patients received immunomodulatory therapy including intravenous immunoglobulin (IVIG), intravenous or oral prednisone, or azathioprine. Statistical analysis encompassed the Fisher exact test or Pearson's chi-square test, with P < 0.5 considered statistically significant.

Among 28 CIDP patients seen over the study period, seven were children (< 16 years) and 21 were adult. Mean age of onset was 9.7 years in the former vs. 51.8 in the

latter, and females predominated in both groups, 57.1% and 71.4%, respectively. Two children had a relapsing course with 1 and 3 episodes, but the remaining five had a monophasic course. Four had motor predominant CIDP, two a sensorimotor type, and 1 a sensory dominant form, with the legs affected in 5, and both arms and legs in two. Prior upper respiratory infection was seen in only two. Cranial nerve involvement was not present in any patient, child or adult. IVIG was used in six children resulting in excellent improvement in all, with two children having a relapse over the 1- to 8-year follow-up period, responding to subsequent steroid therapy with complete, or almost complete, resolution of symptoms. Compared to adults, the children demonstrated more predominant motor involvement of the legs, subacute progression within the first eight weeks, and excellent response to treatment.

■ **COMMENTARY**

Though usually treatment-responsive, not all childhood chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) responds to intravenous immunoglobulin (IVIG), steroid therapy, or plasma exchange (*Eur J Ped Neurol* 2009;13;209-218). When these modalities prove ineffective, azathioprine, methotrexate, or cyclosporine may be beneficial. Anecdotal case reports using interferon α or β, and monoclonal antibodies against specific B-cell antigens including rituximab and alemtuzumab, have also described efficacy in limited instances. Other potential therapies include mycophenolate mofetil, etanercept (tumour necrosis factor alpha antagonist) and tacrolimus (FK-506). Ironically, aside from treating the disorder, interferon-α, β, TNF-α antagonists, and tacrolimus may also cause a demyelinating polyradiculoneuropathy. Nevertheless, CIDP in children has an overall 70%–100% remission rate, as compared to 65%–70% in adults, with a very good outcome in 83%–85%. ■

Transcranial Magnetic Stimulation: New Treatment for Acute Migraine with Aura? Stay Tuned

ABSTRACT & COMMENTARY

By Dara Jamieson, MD

Associate Professor of Clinical Neurology, Weill Cornell Medical College

Dr. Jamieson reports she is a retained consultant for Boehringer Ingelheim, Merck, and Ortho-McNeil, and is on the speaker's bureau for Boehringer Ingelheim and Merck.

Synopsis: *Transcranial magnetic stimulation resulted in improvement in pain-free headache response rates after 2, 24 and 48 hours, as compared to sham stimulation, in patients with acute migraine with aura.*

Sources: Lipton RB, et. al. Single-pulse transcranial magnetic stimulation for acute treatment of migraine with aura: A randomised, double-blind, parallel-group, sham-controlled trial. *Lancet Neurol* 2010;9:373-380. Epub 2010 Mar 4.
Diener HC. Single-pulse transcranial magnetic stimulation: A new way to treat migraine attacks with aura. *Lancet Neurol* 2010;9:335-337. Epub 2010 Mar 4.

Recent use of transcranial magnetic stimulation in depression has led to its evaluation in other disorders of the brain, including migraine. Transcranial magnetic stimulation is a non-invasive technique using a coil of electrical current to apply a pulsed magnetic field to the scalp and cortex, altering neuronal firing. Cortical spreading depression, with a posterior to anterior wave of cortical excitation then inhibition, is a pathophysiological correlate to the initiation of migraine with aura and is a logical target for this technique. This paper reports on an industry-sponsored, randomized, double-blind, parallel-group, two-phase, sham-controlled, multi-center study of single-pulse transcranial magnetic stimulation (sTMS) used to treat an acute attack of migraine with aura. The study of the efficacy and safety of the device was in two parts. There were initially 267 adults with the International Headache Society criteria for migraine with visual aura who were evaluated for their ability to keep a headache diary and recognize the onset of a migraine with aura. In phase two, 201 patients, who were able to comply with the diary and treatment protocol, were randomly allocated by computer to either sham stimulation (n=99) or sTMS (n=102). Participants were instructed to treat up to three attacks over three months while experiencing the migraine aura. Preventative, but not abortive, medications were allowed during the trial. The primary outcome was pain-free response two hours after the first attack, and co-primary outcomes were non-inferiority at two hours for migraine accompanying symptoms of nausea, photophobia, and phonophobia. For the 164 patients who treated at least one attack with sTMS (n=82) or sham stimulation (n=82; modified intention-to-treat analysis set), pain-free response rates after two hours were significantly higher with sTMS (32/82 [39%]) than with sham stimulation (18/82 [22%]), for a therapeutic gain of 17% (95% CI 3-31%; p=0.0179). Sustained pain-free response rates significantly favored sTMS at 24 hours and 48 hours post-treatment. Non-inferiority was shown for nausea,

photophobia, and phonophobia. No device-related serious adverse events were recorded, and incidence and severity of adverse events were similar between the sTMS and sham groups.

■ **COMMENTARY**

Early treatment of migraine with aura by sTMS resulted in increased freedom from pain at two hours compared with sham stimulation, and absence of pain was sustained for up to two days after treatment. The encouraging results of this sTMS study indicate a promising acute treatment for patients with migraine with aura. The use of sTMS for treatment of acute migraine with aura has teleological appeal, as there appears to be a cogent explanation for its effect. This study addresses the major concern of a device trial by using a sham device; but, the stimulation doses and the optimal treatment protocol still need to be determined. Interesting, the commonly noted phenomenon of enhanced efficacy of acute abortive treatment in patients on preventative medication was noted by patients who used the sTMS. As encouraging as these results may be, the majority of migraineurs experience migraine without aura. Cortical spreading depression may also play a role in migraine without aura, expanding the possible use of sTMS; however, timing of initiation of treatment may be problematic without an aura to indicate the migraine headache onset.

In the accompanying editorial, Hans-Christoph Diener, MD pointed out that some research questions are still unanswered and more studies, including a head-to-head comparison with triptans, need to be done. He pointed out the lack of benefit in some secondary endpoints, such as decrease in headache pain from severe-moderate pain to mild-no pain at two hours. However, the results of this well designed trial are encouraging for the millions of migraine sufferers and more investigation is needed. ■

Measuring Regional Brain Tissue Sodium Concentrations in MS

ABSTRACT & COMMENTARY

By Susan Gauthier, DO, MS

Assistant Professor of Neurology and Neuroscience, Weill Cornell Medical College

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

Synopsis: *Higher tissue sodium concentrations were present in multiple sclerosis patients as compared to healthy controls. In patients, sodium levels within lesions corresponded to lesion volumes and grey matter sodium levels were negatively associated with grey matter volume.*

Source: Inglese M, et al. Brain tissue sodium concentration in multiple sclerosis: A sodium imaging study at 3 telsa. *Brain* 2010:133; 847-857.

Changes in axonal membrane architecture have been found to occur in multiple sclerosis (MS) and may be a significant factor leading to a loss of axonal integrity. Redistribution of sodium channels occurs in demyelinated regions of the axons as part of a compensatory change to maintain proper impulse conduction.[1] This process results in an increase in influx of Na^+, which leads to an increase in ATP consumption. The energy depletion impairs the function of Na^+/K^+ ATPase causing an accumulation of axoplasmic Na^+; this in turn is thought to promote the reversal of the Na^+ /Ca^{2+} exchanger. The ultimate consequence of this process is the activation of Ca^{2+} dependent mechanisms that damage the axon. In this recent report by Inglese et al., a novel imaging approach has been proposed to measure regional differences in brain tissue Na^+ in MS patients.

This was a pilot study of 17 relapsing-remitting (RR) MS patients and 13 age/gender matched healthy controls (HC) utilizing ultra-short TE sequences on a 3T Siemens MRI platform. In HC, the tissue sodium concentration (TSC) of grey matter was higher than that of white matter without age or gender differences; a pattern that was reproduced in RRMS patients. TSC of normal appearing white matter (NAWM) was significantly higher in RRMS patients as compared to the white matter of HC; TSC of normal appearing grey matter (NAGM) was similarly higher in patients, although the difference was less remarkable. TSC of lesions hypointense on T1-weighted images and those that enhance with gadolinium were similar, however only the TSC of hypointense lesions was higher than that of T1-isointense lesions. TSC of T1-hypointense lesions were higher than NAWM but similar to NAGM. The TSC of T1-isointense lesions and NAWM were similar, although the TSC of T1-isointense lesions was lower than that of NAGM. The average lesion TSC correlated with both T2 and T1-hypointense lesion volumes; the strongest association was between T1-hypointense lesion TSC and its corresponding lesion volume ($r = 0.47$, $p=0.0003$). Regarding a relationship with brain volume in RRMS patients, the TSC of NAGM had a negative correlation with grey matter volume ($r = -0.23$, $p=0.0009$) but this relationship was not reproduced with NAWM TSC and white matter volume. There was a positive correlation with EDSS and TSC of

T1-hypointense lesions (r = 0.22, p=0.002) and TSC of NAGM (r = 0.20, p=0.002).

■ COMMENTARY

The poor pathological specificity of T2-hyperintense lesions in MS has limited the acceptance of MRI as a biomarker for the disease. However, with higher resolution scanning and sequence development, the pathological specificity of MRI has the potential to significantly improve and sodium imaging represents one of many new MRI techniques under development. There were clear limitations to this study that were fully acknowledged by the authors, the most important of which was the inability to distinguish between intra and extracellular sodium. In addition, given the cross-sectional design of the study, the authors were not able to determine if T1-hypointense lesions were permanent black holes. Permanent T1-hypointense lesions are associated with more axonal loss; however if hypointense lesions are acute or subacute, the pathological specificity is less clear. This is of particular importance given that the majority of the lesions in the study were considered hypointense. There was an interesting association with grey matter TSC and volume; this corresponds well with recent work suggesting grey matter atrophy may be more prominent than white matter atrophy in MS. The modest correlation with disability underscores the complexity of the disease, but this may potentially improve with a larger sample size. Not withstanding these issues, sodium MRI has the potential to be a valuable outcome measure to test novel therapeutics targets in MS, especially for those agents that target the axon membrane architecture.

Reference

1. Dutta R, et al. Pathogenesis of axonal and neuronal damage in multiple sclerosis. *Neurology* 2007;68 (Suppl 3): S22-S31. ■

CME Objectives

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

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

CME Instructions

- Physicians participate in this continuing medical education program by reading the articles, using the provided references for further research, and studying the CME questions. Participants should select what they believe to be the correct answers, then refer to the list of correct answers to test their knowledge. To clarify confusion surrounding any questions answered incorrectly, please consult the source material.
- After completing this activity, participants must complete the evaluation form provided at the end of each semester (June and December) and return it in the reply envelope provided to receive a credit letter. When an evaluation form is received, a credit letter will be mailed to the participant.

CME Questions

53. All of the following regarding treatment of comatose survivors of cardiac arrest with therapeutic hypothermia are true, EXCEPT:

a. Treatment has been shown to improve neurologic outcome.

b. Standard outcome predictors such as somatosensory evoked potentials have been validated during treatment.

c. Treatment often requires the use of sedatives and muscle paralysis.

d. Treatment involves 12-24 hours of induced hypothermia to 32-34 °C.

54. Based on this study, which statement is incorrect?

a. Cognitive impairment and mood disturbances can affect quality of life of patients with PD.

b. Combination of resistance and aerobic exercises are beneficial for frontal lobe based executive functions.

c. Mood was significantly improved by exercise program.

d. Quality of life was not improved by exercise program.

55. Children with chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) respond well to:

a. Intravenous immunoglobulin (IVIG)

b. Steroid therapy

c. Plasma exchange

d. All the above

e. None of the above

56. Transcranial magnetic stimulation in migraine with aura:

a. increases the two-hour pain-free response.

b. was associated with increased risk of chest tightness.

c. shows no benefit in patients on preventative medication.

d. appears to stimulate the trigeminal nucleus. e. has comparable efficacy to triptans.

57. What is the rationale for measuring brain tissue sodium con-

centrations in MS?

a. For the quantification of acute inflammatory activity

b. For the quantification of demyelination

c. To determine response to immunomodulatory therapy

d. Increased intra-axonal sodium may contribute to axonal degeneration; thus a potential indirect measure of neurodegeneration

e. For the quantification of neuronal integrity

58. Use of the ABCB2 score improves prediction of stroke after the occurrence of a TIA

a. True

b. False

59. Intra-arterial thrombolysis does not result in a better outcome compared to control group treatment.

a. True

b. False

60. In patients who are eventually shown to have negative neuroimaging for ischemic stroke, administration of intravenous tPA is still safe.

a. True

b. False

61. Patients with bicuspid aortic valve have a higher rate of intracranial aneurysms than the general population.

a. True*

b. False

Answers: 53. b, 54. c, 55. d, 56. a, 57. d, 58. a, 59. b, 60. a, 61. a.

Stroke Alert: A Review of Current Clinical Stroke Literature

*By **Matthew E. Fink, MD**, Interim Chair and Neurologist-in-Chief, Director, Division of Stroke & Critical Care Neurology, Weill Cornell Medical College and New York Presbyterian Hospital*

Tsivgoulis G, et al. Multicenter external validation of the ABCD2 score in triaging TIA patients. *Neurology* 2010; 74: 1351-1357.

RAPID IDENTIFICATION AND DIAGNOSIS OF PATIENTS WITH TIA is important to prevent subsequent stroke, which occurs in about 10% of all TIA patients in the 90 days following TIA. Half of those strokes occur in the first week following the TIA. The ABCD2 score was developed as a way to stratify patients, based on risk factors, in order to identify which patients should be hospitalized and intensively investigated and monitored. The score is calculated based on the following items: **A**ge > 60 years = 1 point; **B**lood pressure (systolic > 140 or diastolic > 90 = 1 point); **C**linical features (unilateral weakness = 2, speech disturbance without weakness = 1, other symptoms = 0; **D**uration of symptoms (< 10 mins = 0, 10-59 mins = 1, > 60 mins = 2); **D**iabetes mellitus (yes = 1).

The authors studied 148 patients who presented with TIA, applied the ABCD2 score, and followed them for subsequent stroke. The seven-day and 90-day risks of stroke were 8% and 16%. The ABCD2 score accurately discriminated between TIA patients with a high seven-day or 90-day risk of stroke. The 90-day risk of stroke was 7-fold higher in patients with an ABCD2 score of > 3 points. After adjustment for other risk factors that were not part of the score, an ABCD2 score of > 2 was associated with a 5-fold greater 90-day risk of stroke (HR=4.65, 95%CI 1.04-20-84, p=0.045). The score was not able to identify patients who will have a stroke at seven days vs 90 days, requiring that all patients undergo rapid assessment for treatable conditions that might cause a stroke. ■

Lee M, et al. Efficacy of intra-arterial thrombolysis for acute ischemic stroke. Meta-analysis of randomized controlled trials. *Stroke* 2010;41: 932-937.

INTRA-ARTERIAL THROMBOLYSIS (IA) FOR ACUTE ISCHEMIC stroke is widely used throughout the world, but has not been approved by the U.S. Food and Drug Administration (FDA). It remains an important alternative to intravenous thrombolysis because of the improved recanalization of large artery occlusions, and an expanded time window (up to 6 hours). Because no single, randomized, clinical trial (RCT) has demonstrated statistically significant increases in good or excellent outcomes (modified Rankin scores 0-2) compared to the control groups, the authors performed a systematic literature review and meta-analysis of published RCTs that met strict criteria, and combined the results, with special emphasis on good or excellent outcomes.

Their search identified five RCTs with 395 patients comparing IA fibrinolysis with control. IA was associated with increased good outcomes (mRankin 0-2;

OR=2.05, p=0.001) and excellent outcomes (mRankin 0-1; OR=2.14, p=0.003). In addition, there was significant improvement in the NIHSS and the Barthel index in the IA fibrinolysis groups compared to control. Although there was an increased rate of intracerebral hemorrhage in the IA group, this was not associated with an increase in mortality. ■

Chernyshev OY, et al. Safety of tPA in stroke mimics and neuroimaging-negative cerebral ischemia. *Neurology* 2010;74:1340-1345.

RAPID AND WIDESPREAD USE OF INTRAVENOUS TPA FOR treatment of acute ischemic stroke is hampered by fear on the part of emergency department staff of giving the drug to a patient misdiagnosed with ischemic stroke, who ends up with another diagnosis (stroke mimics). The authors addressed this issue by reviewing their stroke registry from 2004–2008 and identifying all patients treated with IV tPA who subsequently had negative imaging.

Among 512 treated patients, 21% were found to not have an infarct on follow-up imaging. In the "stroke mimics" group (14%), average age was 55 years, median NIHSS was 7, and discharge NIHSS was 0, and there were no instances of symptomatic intracerebral hemorrhage. The most common final diagnoses were seizure, complicated migraine, and conversion disorder. In the group identified as "neuroimaging-negative cerebral ischemia" (7%), the average age was greater, but once again, there were no instances of symptomatic intracerebral hemorrhage and all patients had a normal examination at time of hospital discharge. The authors concluded that it is safe to administer tPA to patients who are later diagnosed as "stroke mimics" or TIA. ■

Schievink W, et al. Screening for intracranial aneurysms in patients with bicuspid aortic valve. *Neurology* 2010;74:1430-1433

BICUSPID AORTIC VALVE (BAV) IS A COMMON CONGENITAL heart defect that affects up to 2% of the population. A connective tissue disorder is suspected as a cause for this disorder, which may also involve the intracranial arteries, and the authors therefore screened a group of patients with BAV for the presence of intracranial aneurysms. In a group of 61 patients with BAV (mean age was 48 years, range 29-70), MRA or CTA were used to screen for aneurysms, and compared to an aged-matched control group of 291 people.

Intracranial aneurysms were found in 6 of 61 patients with BAV (9.8%;95% CI 2.4-17.3) and this was significantly higher than in the control group (3/291 or 1.1%, p=0.0012). Known risk factors for intracranial aneurysm development, female sex and advanced age, were more common in the control group. There were no significant differences detected in age, smoking, hypertension, alcohol use, or aortic diameter between the BAV patients with and without aneurysms. BAV patients appear to have a significantly higher rate of intracranial aneurysms and the diagnosis should be considered and pursued in appropriate patients. ■

In Future Issues:

New Treatments for Epilepsy

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By Louis Kuritzky, MD

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Zinc and vitamin C for pressure ulcers?

Source: Jamshed N, Schneider JI. Is the use of supplemental vitamin C and zinc for the prevention and treatment of pressure ulcers evidence-based? *Annals of Long-Term Care: Clinical Care and Aging* 2010;18:28-32.

ELDERLY PATIENTS, PARTICULARLY THOSE residing in nursing homes, are at risk for pressure ulcers (PrU) with recent reviews indicating a nursing home prevalence approximating 10%. Prevention and treatment of PrU commonly includes zinc and vitamin C (Z&C), based upon observations (animal studies) that both are necessary for optimum wound healing. Additional support for this concept comes from recognition of the sometimes marginal nutritional status of senior citizens. Some studies have shown malnutrition to result in an increase risk for PrU by as much as two-fold, but other studies disagree.

For vitamin C, a study performed in the 1970s reported increased wound healing, but the study only contained 20 patients, and subsequent trials have not been able to consistently show similar improvements.

For zinc, one study of senior citizens (n = 672) showed a small but statistically significant difference favoring supplementation, but study design and confounding issues preclude a final word on the subject. Overall, studies have been infrequent, small, and unable to provide a definitive conclusion.

Although generally considered safe, zinc and vitamin C do have associated adverse effect profiles, including increased risk of oxalic acid stones (vitamin C) and copper deficiency (high-dose zinc).

Based upon their literature review, the authors conclude that supplementation of Z&C above recommended dietary intake is not supported, and could have important adverse effects.

Dutasteride reduces prostate cancer risk

Source: Andriole GL, et al. Effect of dutasteride on the risk of prostate cancer. *N Engl J Med* 2010;362:1192-1202.

THE PROSTATE CANCER PREVENTION TRIAL did not ignite advocacy among clinicians for chemoprevention of prostate cancer (PCA). Although this large trial showed an overall reduction in total cancers (about 23%), high-grade tumors were actually statistically significantly increased. Several reasonable explanations for this phenomenon were offered; however, the disquieting consideration that 5-alpha-reductase inhibitors might be efficacious for reduction of low-grade tumors — but not effective for the more important high Gleason score tumors — remained.

Dutasteride and finasteride are very similar in their effects on the prostate, although there are both pharmacokinetic and pharmacodynamic differences. For instance, dutasteride has a much longer half-life (5 weeks), and dutasteride blocks both arms of the 5-alpha-reductase pathway (types 1 and 2), whereas finasteride only blocks type 2. Because both agents are highly efficacious in reducing intraprostatic levels of dihydrotestosterone, the putative culprit in generating BPH and possibly related to development of PCA, many experts consider them clinically comparable.

The REDUCE Trial (Reduction by Dutasteride of Prostate Cancer Events) enrolled men age 50-75 with a PSA of 2.5-10 ng/mL with negative prostate biopsy at baseline. Subjects were randomized to dutasteride 0.5 mg/day or placebo and followed for 4 years, receiving biopsies at year 2 and year 4.

At the completion of the trial, dutasteride was associated with an overall PCA relative risk reduction of 23%; encouragingly, this trial did not show a statistically significantly increased risk of high Gleason score tumors. Because dutasteride also provides favorable symptom benefits for BPH, clinicians may want to re-examine the balance of risks and benefits of 5-alpha-reductase inhibitors.

New short-course topical treatment for actinic keratoses

Source: Swanson N, et al. Imiquimod 2.5% and 3.75% for the treatment of actinic keratoses: Results of two placebo-controlled studies of daily application to the face and balding scalp for two 2-week cycles. *J Am Acad Dermatol* 2010;62: 582-590.

ACTINIC KERATOSES (AKS) RECENTLY HAVE been recognized as both a cosmetic and a dermatopathologic problem, since they are precursors to squamous cell carcinoma. Indeed, current literature suggests that AKs be considered squamous cell carcinoma in situ. AKs treatment includes cryotherapy, excision, chemical destruction (e.g., 5-fluorouracil, diclofenac), immune activation (imiquimod [IMQ]), and others. Because topical treatment courses

are sometimes protracted, and induce unpleasant cutaneous inflammatory changes, clinicians desire simpler, gentler methods.

Swanson et al randomized patients with AKs on the face and scalp to IMQ or placebo (n = 479). IMQ was applied as pulse therapy: qd for 2 weeks, then no treatment for 2 weeks, then repeat (total = 14 days of treatment). Outcomes were measured at 8 weeks.

IMQ produced a 72%-82% reduction in AKs lesions; higher doses produced complete clearing in 59% (vs 6% with placebo). A companion article in the same journal showed similar clearance rates for a longer regimen (3-week treatment courses). This simpler regimen was well tolerated, and provides a quick and effective route for topical treatment of AKs.

After bariatric surgery: The role of exercise

Source: Evans RK. Maintaining weight loss momentum after bariatric surgery. *Am J Lifestyle Med* 2010;4:124-127.

Bariatric surgery is increasingly recognized as a rational therapeutic option for morbid obesity and obese patients with comorbidities such as diabetes. On average, bariatric surgery produces a 35% reduction in body weight, but patients regain varying amounts of weight over time. Studies of the role of diet after bariatric surgery have helped to direct long-term postoperative dietary management, but less information is available to guide exercise advice.

In the period after postoperative weight-loss stabilization, the weekly amount of exercise does correlate with sustained weight loss. Unfortunately, 37%-51% of postoperative subjects have been found to be noncompliant with exercise recommendations. Curiously, adherence to exercise in some trial data was greater before surgery than afterward, as if subjects felt they no longer needed exercise to the same degree now that surgery had been performed.

Bariatric surgery does not completely and permanently resolve weight-management issues in obese subjects. The high frequency with which post-surgical patients are noncompliant with exercise recommendations, with anticipated weight gain consequences, should spur clinicians to bolster patient education.

What aspect of HTN produces toxicity?

Source: Rothwell PM, et al. Prognostic significance of visit-to-visit variability, maximum systolic blood pressure, and episodic hypertension. *Lancet* 2010;375:895-905.

A well-established body of epidemiologic literature supports a continuous graded risk between systolic blood pressure (SBP) and CV risk. This relationship has held constant whether one considers office BP, home BP, or ambulatory blood pressure monitoring (ABPM). Because BP is variable over time, it is unclear whether the toxicity of BP to the vasculature is more strongly associated with mean BP, maximum BP, pulse pressure (SBP − DBP), or BP variability. Circadian rhythm of BP has also been recognized to be particularly associated with adverse outcomes: ABPM subjects whose BP does not decline overnight (called non-dippers) have greatly increased CV risk, well beyond what would be expected simply by having a greater total number of hours of exposure to elevated BP.

Rothwell et al used a data set comprised of persons who had sustained a TIA in large clinical trials (n = 2006), including the UK TIA Trial and ASCOT. Visit-to-visit BP variability and maximum SBP were better predictors of adverse outcome than mean SBP. Similarly, persons with episodic HTN (normal BP on some occasions, elevated on others) were also at increased stroke risk, surpassing risk for stable BP.

It remains to be elucidated why these subgroups of individuals with BP variability have a greater risk burden. Although the associations between maximum SBP, BP variability, and episodic BP elevations were consistent, this does not establish causation. Perhaps the strongest cautionary message from this trial is that clinicians should not fall prey to false reassurance when they see a mixed BP response pattern including some BP measurements at goal and others elevated; such episodic elevations are consequential.

Depression and sleep disturbance

Source: Van Mill JG, et al. Insomnia and sleep duration in a large cohort of patients with major depressive disorder and anxiety disorders. *J Clin Psychiatry* 2010;71:239-246.

Both anxiety and depression disorders have a strong association with sleep disturbance. The association between sleep and depression is bidirectional: Depression is often manifest by or leads to sleep disturbance, and persistent insomnia increases risk of depression.

Van Mill et al sought to elucidate further the relationship between sleep disorders and depression by analyzing subjects in the Netherlands Study of Depression and Anxiety cohort (n = 2619).

In this population of subjects (approximately three-fourths suffered from depression and/or anxiety), almost half scored at least 9 on the Insomnia Rating Scale (IRS; the same metric that was employed in the Women's Health Initiative), fulfilling criteria for clinically significant insomnia. Insomnia scores were related to both anxiety and depression, but worse for depression, and highest for comorbid depression and anxiety. Interestingly, even persons with depression or anxiety in remission had elevated scores on the IRS. The authors suggest that, based upon their data, inquiry into sleep status is valuable not only during both depression and anxiety, but even during periods of remission.

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Atypical Fractures and Bisphosphonate Therapy

In this issue: Fractures and bisphosphonate therapy, warfarin anticoagulation and influenza vaccine and cotrimoxazole, antiplatelet therapy with clopidogrel and aspirin, FDA Actions.

Bisphosphonates and atypical fractures

Atypical fractures of the femur have been linked with bisphosphonate therapy in several recent news stories. A recent industry-sponsored study looks to quell these concerns. Secondary analysis from three large randomized bisphosphonate trials with more than 14,000 women showed that among 284 hip or femur fractures recorded, a total of 12 fractures in 10 patients were classified as occurring in the subtrochanteric or diaphyseal femur, a combined rate of 2.3 per 10,000 patient years. As compared with placebo, the relative hazard ratio for the three trials did not meet statistical significance, although confidence intervals were wide. The authors conclude that the occurrence of fracture of the subtrochanteric or diaphyseal femur was very rare even among women who had been treated with bisphosphonates for as long as 10 years (*N Engl J Med*; published on-line March 24, 2010). An accompanying editorial published on-line at the same time by Elizabeth Shane, MD, Columbia University, acknowledges that despite excellent safety profiles, bisphosphonates have been associated with "atypical" fractures of the femur that occur with minimal or no trauma, generally affecting the proximal third of the femoral shaft. Most of these fractures have occurred in women on long-term alendronate therapy, occasionally taken together with other antiresorptive drugs, corticosteroids, or proton pump inhibitors. Shane points out that while these fractures represent concern, they are uncommon and actually occur more frequently in patients who are not on bisphosphonates. The results of this study "provide assurance that subtrochanteric fractures are extremely rare" and many more hip fractures are "prevented by bisphosphonates than are potentially caused by the drugs." Treatment with bisphosphonates up to 10 years is more effective than shorter-term treatment in preventing new vertebral fractures and nonvertebral fractures, but she also suggests that patients should be considered for "drug holidays with careful observation" if they have been on long-term therapy.

Warfarin, flu vaccine, and cotrimoxazole

Anticoagulation with warfarin requires careful monitoring. Concomitant use of medications may result in changes in the international normalized ratio (INR), which may increase the risk of bleeding or decrease the effectiveness of therapy. Two studies in the April 12 issue of *Archives of Internal Medicine* clarify the risk of two commonly used medications, influenza vaccine and the antibiotic trimethoprim-sulfamethoxazole. Patients on warfarin have been told that they need careful monitoring after the influenza vaccine, although the effect is not clear. Some guidelines have suggested that flu shots prolonged INRs, while others suggest the vaccine reverses the anticoagulation effect.

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In this study, 104 patients on a stable warfarin regimen were randomized to receive influenza vaccine and subsequent placebo administration or vice versa. All patients were tested for coagulation variables and followed for clinical events. The influenza vaccine had no effect on anticoagulation compared to placebo. There were no fatal or major bleeding events. The authors conclude that the influenza vaccine has no significant effect on INR values or warfarin weekly doses in patients on chronic warfarin therapy and that close monitoring of INR values after influenza vaccine is not required (*Arch Intern Med* 2010;170:609-616).

Conversely trimethoprim-sulfamethoxazole (cotrimoxazole) may significantly prolong INRs with adverse clinical outcomes. In the population-based, nested case-controlled study using health care databases in Canada, residents 66 years or older who were treated with long-term warfarin were evaluated for upper gastrointestinal (GI) tract hemorrhage. Of the more than 134,000 patients on warfarin, 2151 patients were hospitalized for upper GI hemorrhage. Recent use of cotrimoxazole was almost four times more common in those hospitalized (adjusted odds ratio, 3.84; 95% CI, 2.33-6.33). The odds ratio for treatment with ciprofloxacin also was higher (1.94), but no significant association was observed with amoxicillin, ampicillin, nitrofurantoin, or norfloxacin. The authors conclude that among older patients receiving warfarin, cotrimoxazole is associated with a significantly higher risk of upper GI tract hemorrhage. Ciprofloxacin was also associated with risk and whenever possible clinicians should prescribe alternate antibiotics in patients receiving warfarin (*Arch Intern Med* 2010;170:617-621).

Clopidogrel and aspirin

What is the optimal duration of dual antiplatelet therapy with clopidogrel and aspirin in patients with drug-eluting stents? In previous studies, early discontinuation of dual antiplatelet therapy has been identified as a risk factor for late stent thrombosis. A new study seeks to determine whether dual antiplatelet therapy for more than 1 year is of value. In a study that merged data from two concurrent randomized, clinical trials, 2701 patients who had received drug-eluding stents and had been free of major adverse cardiac events, cerebrovascular events, or major bleeding for a period of at least 12 months were randomized to receive clopidogrel plus aspirin or aspirin alone. The primary endpoint was a composite of myocardial infarction (MI) or death from cardiac causes. The cumulative risk of the primary outcome at 2 years was 1.8% with dual antiplatelet therapy as compared with 1.2% with aspirin monotherapy (hazard ratio, 1.65; 95% confidence interval, 0.80-3.36; $P = 0.17$). The individual risks of MI, stroke, stent thrombosis, need for repeat revascularization, major bleeding, and death did not differ significantly between the two groups. However, there was a trend toward higher risk for these outcomes in the dual therapy group ($P = 0.051$ for MI, stroke, or death from any cause; $P = 0.06$ for MI, stroke, or death from cardiac cause). The authors conclude that use of dual antiplatelet therapy for longer than 12 months is not more effective than aspirin alone in patients who have received drug-eluding stents (*N Engl J Med* 2010; 362:1374-1382).

FDA Actions

Rifaximin, Salix Pharmaceutical's minimally absorbed (nonsystemic) oral antibiotic has been approved to reduce the risk of recurrent hepatic encephalopathy in patients with advanced liver disease. Rifaximin was previously approved to treat traveler's diarrhea. The drug, which is taken orally twice a day, appears to reduce ammonia levels by reducing gut flora. It is marketed as Xifaxan®.

The FDA has approved Pancreaze, a new pancreatic enzyme product for patients who do not produce enough pancreatic enzymes (due to cystic fibrosis, chronic pancreatitis, pancreatic surgery, etc.). Pancreaze is the third approved pancreatic enzyme product on the market after Abbott's Creon® and Eurand's Zenpep®. The approval coincides with the FDA's deadline to cease marketing unapproved pancreatic enzyme products that have been available for many years. In October 2007, the FDA announced a deadline of April 28, 2010, after which time unapproved products would no longer be available.

The FDA has approved the first generic version of the popular antihypertensive losartan (Cozaar®) as well as the combination of losartan and hydrochlorothiazide (Hyzaar®). This represents the first generic angiotensin receptor blocker on the market, a development that has been anxiously awaited by consumers. Losartan carries a boxed warning against using the drug during pregnancy. Generic losartan is available in 25 mg, 50 mg, and 100 mg strengths, while losartan/hydrochlorothiazide is available in 50 mg/12.5 mg, 100 mg/12.5 mg, and 100 mg/25 mg strengths.

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