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INSIDE

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Treating Active Neuromyelitis Optica with Mitoxantrone

ABSTRACT & COMMENTARY

By Susan Gauthier, DO, MPH

Assistant Professor of Neurology and Neuroscience, Weill Cornell Medical College

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

Synopsis: *Twenty highly active patients with neuromyelitis optica (NMO) stabilized after treatment with mitoxantrone. All patients tolerated treatment without significant safety concerns. Mitoxantrone may be an option for NMO given its differential inhibitory effect on subsets of B-cells.*

Source: Kim S, Woojun K, Park M, et al. Efficacy and safety of mitoxantrone in patients with highly relapsing neuromyelitis optica. *Arch Neurol* 2010; Dec13 (epub ahead of print).

NEUROMYELITIS OPTICA (NMO) IS AN INFLAMMATORY DISEASE OF THE CENTRAL nervous system that is thought to be primarily B cell mediated given the presence of anti-aquaporin 4 autoantibodies in the serum of the majority of patients. The clinical manifestations of NMO are relapsing episodes of optic neuritis and multi-segmented inflammatory lesions within the spinal cord, wherein patients accumulate a significant amount of disability within a short period of time. Patients with NMO traditionally have been treated with a similar approach as patients with relapsing multiple sclerosis (MS); however, NMO patients have a poor response to standard immunomodulatory therapy (interferon beta or glatiramer acetate). Through the recent advancement regarding the pathogenesis of NMO, the treatment strategy has shifted to treating the disease with B cell specific agents. As a result of this paradigm switch, Kim et al reported on 20 highly active NMO patients treated with mitoxantrone and studied the selective B cell inhibitory mechanisms induced by this treatment.

Patients selected for this retrospective study either met the diagnostic criteria for NMO or NMO spectrum disorder and had at least two relapses within the year prior to treatment. The monthly induction protocol

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varied between 3 to 6 months followed by an every 3-month infusion to a maximum treatment dose of 100-120 mg/m^2. Baseline relapse rate and EDSS (disability score) was compared to follow-up post-treatment scores, wherein the mean follow-up was 17 months after the start of treatment. The median annualized relapse rate was reduced from 2.8 to 0.7 ($P < 0.001$) and mean EDSS improved from 5.6 to 4.4 ($P < 0.001$). Patients tolerated the treatment without significant infections. One patient had an asymptomatic decrease in ejection fraction (64% to 54%) and there was no therapy-related acute leukemia in a mean safety follow up of 41 months. To study changes within specific leukocyte subsets after six monthly infusions, 10 patients had serum collected for a flow cytometric analysis. CD19$^+$ B cells were selectively decreased after treatment with mitoxantrone as compared to T cell subsets. Among B cells, mitoxantrone preferentially decreased CD27$^+$ memory B cells as compared to CD27$^-$ naive B cells.

■ COMMENTARY

Mitoxantrone is a known effective antineoplastic agent that blocks DNA synthesis and impairs DNA repair. It is currently the only FDA-approved intravenous immunosuppressant for the treatment of relapsing forms of MS. Although mitoxantrone has a broad immunosuppressive effect, multiple studies throughout the years have demonstrated that it has a profound effect on the humoral immune system, yet how this relates to its beneficial effect in MS is unknown. Unfortunately the use of mitoxantrone in the treatment of MS has been limited by its cardiac toxicity and a more recently reported treatment-associated acute leukemia. Nevertheless, given the limited treatment options for NMO and the aggressive nature of the disease, there is a rationale to consider higher risk therapeutics, such as mitoxantrone, to stabilize actively relapsing NMO patients. The current report was a small retrospective study; therefore we can only conclude that mitoxantrone potentially may stabilize active NMO patients. However, the authors were able to show that mitoxantrone preferentially inhibited memory B cells in this population. Putting this together, it is reasonable to consider mitoxantrone for active NMO patients, although as the authors acknowledge, it remains to be determined if short-term treatment with mitoxantrone will provide long-term stabilization. In addition, considering the risk of this drug, it would be difficult to recommend it as first-line therapy. The authors suggested a potentially safer alternative treatment protocol, which is a 6-month induction of mitoxantrone followed by a less toxic immunosuppressant for maintenance; however, this will need to be evaluated further. More selective B cell agents, such as rituximab, also are being studied in NMO and are considered to be a more tolerable and targeted treatment strategy. Safety issues related to the chronic use of this drug have not been explored. ■

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Early Aggressive Therapy for Myasthenia Gravis

ABSTRACT & COMMENTARY

By Michael Rubin, MD

Professor of Clinical Neurology, Weill Cornell Medical College

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

Synopsis: *Early plasmapheresis and high-dose intravenous corticosteroids may be as effective as conventional oral corticosteroid therapy in the treatment of myasthenia gravis.*

Source: Nagane Y, Suzuki S, Suzuki N, Utsugisawa K. Early aggressive treatment strategy against myasthenia gravis. *Europ Neurol* 2011;65:16–22 DOI: 10.1159/000322497.

CAN EARLY AGGRESSIVE THERAPY (EAT) IMPROVE THE LONG-term outcome of newly diagnosed myasthenia gravis (MG)? EAT was defined as a single plasma exchange, followed by 1 g intravenous methylprednisolone, immediately, and on the two subsequent mornings, followed

by low-dose oral corticosteroids to maintain clinical improvement. To assess the efficacy of EAT, a retrospective analysis of patients with new-onset, generalized MG, was undertaken, and patients treated with the EAT protocol were compared to new-onset MG patients treated with high-dose oral prednisone alone, administered in a conventional fashion (10-20 mg per day and slowly increasing the dose on a weekly basis by 5-10 mg per day, to a maximum of 1 mg/kg per day). Patients were maintained on this dose until maximum improvement was appreciated. Prednisone then was tapered, on a monthly basis, by 20% of the previous daily dose. Pyridostigmine bromide was given as needed. Inclusion criteria required having received treatment for at least 1 year with continued follow-up, and availability of complete medical records, including clinical severity scores, comprising the quantitative MG (QMG) score or the quantified MG strength (QMGS) score. Exclusion criteria for EAT included having received plasma exchange, intravenous immunoglobulin, or high-dose methylprednisolone in the absence of myasthenic crisis; not having received maximum prednisone dosage due to side effects; or having received oral prednisone for uncontrolled symptoms. Statistical analysis was provided using the Mann-Whitney U test for continuous variables, the X^2 test for categorical variables, and the Wilcoxon signed-ranks test, with $P < 0.05$ considered statistically significant.

Among 410 new-onset MG patients seen at Hanamaki General Hospital and Keio University Hospital in Tokyo, Japan, between April 1995 and November 2009, 281 were diagnosed with generalized MG, of which 76 received EAT and 81 received high-dose oral prednisolone therapy. Of these, 49 EAT patients and 22 high-dose oral prednisolone patients satisfied entry criteria and served as the basis for this retrospective study. EAT patients demonstrated marked early improvement with lower subsequent oral prednisone dosage requirements compared to the high-dose prednisolone group, and minimal manifestations of disease were seen in the EAT group at 1 year and at final observation at 4.1 years. Both new-onset diabetes and moon facies were less frequent in the EAT group but additional short-term hospitalizations were required in this group for additional EAT to maintain remission. EAT may have some advantages over high-dose oral prednisone but these may be outweighed by the disadvantages of requiring repeated hospitalizations. As a retrospective study, the above findings need to be replicated in a prospective, randomized treatment trial comparing the two regimens.

■ COMMENTARY

Patients with generalized myasthenia also benefit from thymectomy, regardless of whether a hyperplastic or atrophic thymus is present.[1] Among 175 myasthenia patients who underwent trans-sternal thymectomy between 1990 and 2004, 128 had hyperplastic and 47 had atrophic thymus glands. Median time to remission was similar in both groups (4.8 vs. 4.9 years) but median time to clinical improvement was 1 year longer ($P = 0.005$) in the atrophic thymus group, which also demonstrated more ectopic thymus in the anterior mediastinum. Both hyperplastic and atrophic thymus tissue exhibited increased B-cell activating factor receptor, CD19, and CD21. Thymectomy is warranted for MG patients even in the presence of an atrophic thymus. ■

Reference

1. Chen Z, Luo H, Peng Y, et al. Comparative clinical features and immune responses after extended thymectomy for myasthenia gravis in patients with atrophic versus hyperplastic thymus. *Ann Thorac Surg* 2011;91:212-218.

Hold Your Applause! A Critical Reappraisal of the Applause Sign

ABSTRACT & COMMENTARY

By Melissa J. Nirenberg, MD, PhD

Assistant Professor, Neurology and Neuroscience, Weill Cornell Medical College

Dr. Nirenberg reports that she has consulted for Biovail.

Synopsis: *The applause sign is a nonspecific indicator of frontal lobe dysfunction and is not specific to Parkinsonian disorders.*

Source: Luzzi S, Fabi K, Pesallaccia M, et al. Applause sign: Is it really specific for Parkinsonian disorders? Evidence from cortical dementias. *J Neurol Neurosurg Psychiatry* 2011; doi:10.1136/jnnp.2010.224394.

In 2005, a study published in *NEUROLOGY* demonstrated the usefulness of a simple bedside test, known as the "three clap test," in distinguishing progressive supranuclear palsy (PSP) from both frontotemporal dementia (FTD) and idiopathic Parkinson's disease (PD).[1] The test consists of asking the patient "to clap three times as quickly as possible after demonstration of the examiner." When patients clap more than three times, an "applause sign" is present; this is felt to be a sign of motor perseveration and/or apraxia. The authors of this prior study found that the applause sign occurred commonly in PSP and was absent from those with PD or FTD, and therefore concluded that the test is useful for distinguishing between these disor-

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*

High Systolic Blood Pressure upon Stroke Admission Associated with Higher Mortality

Source: Geeganage C, Tracy M, England T, et al. Relationship between baseline blood pressure parameters (including mean pressure, pulse pressure, and variability) and early outcome after stroke. Data from the Tinzaparin in Acute Iscaemic Stroke Trial (TAIST). *Stroke* 2011;42:491-493.

Controversy remains regarding the optimal blood pressure early in the course of ischemic stroke. The investigators looked back at the TAIST trial admission blood pressure data on 1,479 patients to determine if there were hemodynamic variables that had an impact on subsequent morbidity and mortality. Baseline systolic BP, mean BP, heart rate, pulse pressure (PP), and systolic BP variability were correlated with the following outcomes—death, neurologic deterioration, death or deterioration, and stroke recurrence. Binary logistic regression with adjustment for baseline prognostic factors, time to treatment, and treatment assignment were performed.

At day 10, death or neurologic deterioration was associated with systolic BP (adjusted odds ratio [OR] = 1.02; 95% confidence interval [CI], 1.01-1.03), mean arterial pressure (OR = 1.02; 95% CI, 1.01-1.04), pulse pressure (OR = 1.02; 95% CI, 1.01-1.03), and BP variability (OR = 1.03; 95% CI, 1.01-1.05). The data suggest that these hemodynamic parameters may be potential therapeutic targets to improve outcome after ischemic stroke. ■

Should Statins Be Avoided After Intracerebral Hemorrhage?

Source: Westover MB, Bianchi MT, Eckman MH, Greenberg SM. Statin use following intracerebral hemorrhage. A decision analysis. *Arch Neurol* 2011. doi:10.1001/archneurol.2010.356.

Statins are used widely for both primary and secondary prevention of ischemic cardiovascular disease and stroke. Recent studies have suggested that there may be an increased risk of intracerebral hemorrhage (ICH) with very low levels of LDL as well as the use of high doses of a statin. In order to assess the possible hazard of using a statin in patients who have already sustained an ICH, the authors created a simulated clinical trials model (Markov model), using a computer program that calculates the risk of recurrent ICH, based on the location of the hematoma (deep or lobar) and the presence of other risk factors, such as hypertension and dementia. The main outcome measure was life expectancy, measured as quality-adjusted life-years (QALYs).

Continued on page 53

ders. A subsequent study concluded that the three clap test was not specific for PSP, but instead was a highly specific marker of Parkinsonian disorders in general.[2]

In the current study, the authors reexamined the applause sign, with the goal of determining whether the sign also may occur in neurodegenerative disorders that spare the basal ganglia, such as Alzheimer's disease (AD) or FTD without parkinsonism. The authors evaluated for the presence of the applause sign in 77 subjects—10 with PSP, 15 with sporadic behavioral variant FTD, 29 with AD, and 23 healthy controls. Neurological diagnoses were determined based on standard clinical diagnostic criteria. A secondary goal of the study was to test the hypothesis that the applause sign is a marker for motor perseveration rather than apraxia; for this reason subjects with apraxia were excluded from enrollment. In addition, all studies underwent neuropsychiatric testing to determine the characteristics that correlated with the presence of an applause sign.

The authors found that the applause sign occurred in all of the neurodegenerative disorders that were examined (80% in PSP, 70% in FTD, and 31% in AD), and they were able to distinguish subjects with neurodegenerative disease from healthy controls. The three clap test also distinguished between PSP and AD. There were no statistically significant differences when comparing PSP with FTD, nor were there differences when comparing FTD with AD. The presence of an applause sign correlated with executive dysfunction on neuropsychiatric testing. Based on their findings, the authors conclude that the applause sign is a nonspecific sign of frontal lobe dysfunction that occurs not only in basal ganglia disorders, but also in cortical dementias such as AD.

■ COMMENTARY

Rapid, simple bedside tests—particularly those with high specificity and sensitivity—are highly coveted tools in the field of neurology. For this reason, there was much excitement when it was originally reported that the three clap test could distinguish most cases of PSP from either

Stroke Alert (continued)

After ICH, the avoidance of statins was favored in this computer model, particularly in survivors of lobar ICH who are at the highest risk for recurrent ICH. Survivors of ICH, who have no other cardiovascular events, gain 2.2 QALYs if they avoid statins. In patients who had a lobar ICH and prior cardiovascular events, the annual risk of heart attack would have to exceed 90% to favor statin therapy. Even survivors of deep ICH appear to have a survival benefit by avoiding statins. Because this study is based on a computer model, a real-life cohort study or case-control study is needed before any treatment recommendations can be made regarding statins. ■

Patients with Ischemic Strokes Have Lower Mortality if Treated at a Certified Stroke Center

Source: Xian Y, Holloway RG, Chan PS, et al. Association between stroke center hospitalization for acute ischemic stroke and mortality. *JAMA* 2011;305:373-380.

THE JOINT COMMISSION BEGAN CERTIFICATION OF STROKE centers, based on the Brain Attack Coalition (BAC) recommendations, in 2003. New York, Massachusetts, and Florida have developed their own designation program also using the BAC criteria. However, data collection and monitoring of these programs all have been based on process measures, such as "door-to-CT scan" time and use of thrombolytics. In order to assess the impact of stroke centers on mortality, the investigators reviewed hospital data from the New York Statewide Planning and Research Cooperative System (SPARCS) for 33,090 adult patients with a principal diagnosis of acute ischemic stroke between January 1, 2005 and December 31, 2006. By the end of 2006, 104 (42.6%) of 244 New York hospitals became state-designated stroke centers, and these hospitals were compared to non-designated hospitals.

As the primary outcome measure, the investigators examined 30-day all-cause mortality, and secondary outcome measures were 1-day, 7-day, and 1-year all-cause mortality. Among 30,947 acute ischemic stroke patients, 15,297 (49.4%) were admitted to designated stroke centers, and this selective admission was associated with a lower 30-day all-cause mortality (10.1% vs. 12.5%; $P < 0.001$), and greater use of thrombolytic therapy (4.8% vs. 1.7%; $P < 0.001$). Differences in mortality were observed at 1-day, 7-day, and 1-year follow-up, and these differences were specific for stroke, as there were no differences in mortality between center-type for patients with other diagnoses, including GI hemorrhage or acute myocardial infarction. Among patients with acute ischemic stroke, admission to a designated stroke center was associated with lower mortality. ■

FTD or PD. Unfortunately, subsequent studies have failed to fully replicate these initial compelling findings.

In the current study, the authors ask the straightforward question of whether the applause sign is specific to basal ganglia disorders. Their findings demonstrate that this sign also may occur in cortical dementias without apparent basal ganglia involvement, correlating mainly with executive dysfunction. However, the applause sign was of some utility in distinguishing between PSP and AD. Thus, although the applause sign is not 100% specific to basal ganglia disorders, it is a useful marker of executive dysfunction, which is often a prominent feature of PSP.

The authors' findings are interesting and clinically relevant, but the study itself has a number of important methodological limitations. The first is the fact neurodegenerative disorders were diagnosed clinically, such that some subjects may have been miscategorized. Second, the authors looked exclusively at sporadic behavioral variant FTD, which has more prominent executive dysfunction (and overlap with PSP) than other FTD subtypes; the findings therefore should not be extrapolated to other forms of FTD. Third, the sample size was low, such that the study may have lacked the necessary statistical power to demonstrate differences between groups. For this reason, further studies with a larger sample size and confirmatory diagnostic tests are warranted.

In summary, this study shows that the applause sign is a strong indicator of frontal lobe dysfunction that is present not only in basal ganglia disorders but also in cortical dementia. Further study is needed to clarify the sensitivity and specificity of this test in distinguishing between specific neurodegenerative disorders. ■

References

1. Dubois B, Slachevsky A, Pillon B, et al. "Applause sign" helps to discriminate PSP from FTD and PD. *Neurology* 2005;64: 2132-2133.
2. Wu LJ, Sitburana O, Davidson A, et al. Applause sign in Parkinsonian disorders and Huntington's disease. *Mov Disord* 2008; 23:2307-2311.

Is Vitamin D Important in the Prevention of Dementia?

ABSTRACT & COMMENTARY

By Michael Lin, MD

Associate Professor of Neurology and Neuroscience, Weill Cornell Medical College

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

Synopsis: *Severe Vitamin D deficiency appears to worsen dementia and supplementation may be beneficial.*

Sources: Llewellyn DJ, Lang IA, Langa KM, et al. Vitamin D and risk of cognitive decline in elderly persons. *Arch Intern Med* 2010;170:1135-1141. Evatt ML. Vitamin D and cognitive decline in elderly persons: Further details. *Arch Neurol* 2010;67:1513-1515.

Vitamin D recently has been associated with a range of conditions other than osteopenia, including neurologic diseases such as multiple sclerosis. There is also reason to suspect that vitamin D may play a role in cognitive decline. Several previous cross-sectional studies have found an association between vitamin D and cognition in elderly subjects, although this finding has not been consistent. Llewellyn and colleagues have now published the first prospective study examining vitamin D and cognition in elderly subjects, and found that low vitamin D levels were associated with increased risk of substantial cognitive decline.

The authors examined adults 65 years or older enrolled in the InCHIANTI study, a prospective population-based cohort study conducted in Tuscany between 1998 and 2006, with follow-up assessments every 3 years. A total of 858 subjects consented and completed blood draws and at least one follow-up assessment, with a mean (± SD) follow-up of 5.2 ± 1.3 years. The study measured 25-hydroxyvitamin D (25(OH)D) levels, and cognition assessed using the Mini-Mental State Exam (MMSE) and Trail Making Tests A and B. Substantial decline was defined as a drop of 3 or more points on the MMSE, or the worst 10% of the distribution of decline on the Trail Making Tests, or discontinuation due to excessive mistakes.

The relative risk of substantial decline on the MMSE in subjects with severe vitamin D deficiency (25(OH)D < 25 nM) compared to subjects with sufficient vitamin D levels (25(OH)D ≥ 75 nM) was 1.60 (95% confidence interval [CI] 1.19-2.00). For the same groups, the relative risk of substantial decline on Trails B was 1.31 (95% CI 1.03-1.51). For both the MMSE and Trails B, the *P* values for a linear trend were statistically significant, suggesting a dose-response relationship. No association was seen for Trails A. All associations remained significant after extensive adjustment for confounding factors that might affect cognition or vitamin D levels (age, sex, education, baseline cognitive score, season tested, smoking, depression, body mass index, alcohol consumption, caloric intake, vitamin E level, mobility) or factors that might potentially mediate an association between vitamin D and neurologic status (stroke, diabetes, hypertension).

■ COMMENTARY

This study has a number of strengths. It is the first prospective study of vitamin D and cognition in elderly subjects, with straightforward design and well-recognized endpoints. It was large, and the investigators were able to adjust for a wide range of confounding variables. In particular, it is unlikely that the observed association was due to reverse causation; i.e., that baseline dementia or impaired mobility reduced vitamin D levels by affecting diet or exposure to sunlight. On the other hand, the study was geographically confined, and all participants were of white European origin. Replication in other locales and populations is necessary. Moreover, the specific causes of cognitive decline were not assessed.

The authors review a number of biologic studies implicating vitamin D in neurologic function and supporting its potential involvement in neurodegeneration. Neurons and glia express vitamin D receptors and enzymes involved in vitamin D metabolism. Vitamin D affects neuronal calcium levels, reduces oxidative stress by inhibiting inducible nitric oxide synthase and increasing glutathione levels, and regulates the synthesis of neurotrophic factors and stimulates neurogenesis. Vitamin D is an immunosuppressor and may reduce autoimmune damage. Vitamin D also stimulates Aβ phagocytosis and clearance by macrophages, and protects against apoptosis. On the other hand, caution is necessary, as excessive vitamin D intake has a number of adverse effects, including renal toxicity and potentially pancreatic cancer. ■

Which Way is Up?

ABSTRACT & COMMENTARY

By Marc Dinkin, MD

Assistant Professor of Ophthalmology, Weill Cornell Medical College

Dr. Dinkin reports no financial interest in this field of study.

Synopsis: *A novel technique used to study deviations*

in the subjective visual vertical may assist in the localization of brainstem lesions.

Source: Frisén L. Deviations of the visual upright in three dimensions in disorders of the brainstem: A clinical exploration. *Brain* 2010;133:3541-3551.

Deficits in the ability to determine one's position relative to the field of gravity are not uncommon in patients with neurological disease, and yet they often go undetected and may be underestimated in terms of their effect on patients' daily quality of life. In fact, it has been shown that 94% of patients with brainstem damage suffer from a deviation in their perception of what is straight up ("the subjective visual vertical" or SVV) in either the roll plane (rotating around an axis through one's stomach) or pitch plane (rotating around an axis extending from one hip to another). It follows that measuring a patient's sense of the SVV might help diagnose brainstem disease and even aid in localization. The bulk of prior studies have focused on deviations in roll, since they are parallel to ocular torsional movements, and since an association between imbalanced utricular-vestibular tone and the pathological ocular tilt reaction (OTR) has been well described. Deviations in perception of pitch were examined by Wikkels several years ago using a self-illuminated rod that was fixed in the sagittal plane and could be pushed forward and backward, in patients with hydrocephalus, with inconclusive results.

In a recent article in *Brain*, Lars Frisén studied 176 patients with neurological disease, using a similar self-illuminated rod that could be tilted along both the roll and pitch axes, in complete darkness, in an attempt to examine deviations in the SVV in three dimensions and their correlation with neuro-anatomical localization.

Although control subjects showed almost no deviation in pitch, many patients with diffuse neurodegenerative disease (Parkinson disease and progressive supranuclear palsy [PSP]) showed an abnormal sense of pitch (defined as $\geq \pm 4°$), but the direction of deviation could not be predicted based on disease. Interestingly, those patients in the obstructive hydrocephalus and pineal pathology groups tended to show negative deviations in pitch, with a shared downstream effect of dorsal midbrain compression proposed as an explanation for this common finding. Patients with cerebellar or craniocervical junction lesions also tended to show negative deviations in pitch, while medullary lesions typically produced positive deviations. Midbrain and pontine lesions varied, although analysis of a subset in the midbrain group suggested that ventral lesions were associated with positive deviations and dorsal lesions with negative deviations. Surprisingly, the degree of deviation in pitch did not correlate with limitations of vertical gaze in patients with the dorsal midbrain syndrome or PSP, implying that there is a separate substrate for static positioning and dynamic eye movements along the pitch axis.

In looking at deviations in roll, the only anatomical correlation was that laterally placed focal brainstem lesions tended to produce ipsiversive deviations in roll, in line with our current understanding of the neural substrate of the ocular tilt reaction. In general, the absolute value of deviation in pitch did not correlate well with that of roll, but in patients with the ocular tilt reaction, there was actually a tight correlation. How can this be explained? The author proposed a geometrical model to explain this phenomenon: Assuming a degree of convergence, the vertical planes of the two eyes overlaps in a vertical line at some point in the distance. Since, in patients with OTR, the degree of torsion typically is not symmetric between the two eyes, some extorsion or intorsion ensues. In the case of extorsion, the line of intersection of the two eyes' vertical planes tilts forward, and with intorsion, it tilts backwards, thus explaining how a greater deviation in roll (assumed to correlate with a larger difference in roll between the two eyes) would in turn cause a greater deviation in pitch.

The author supports this model by pointing out that an observer with a Maddox rod in front of each eye looking at a point source of light will perceive a forward pitch of the line produced when both rods are extorted and vice versa. It is then suggested that double Maddox rod testing could be used as a bedside clinical assay for deviations in roll and pitch simultaneously.

■ COMMENTARY

This appears to be one of the first studies to look at combined deviations in multiple planes at once in a large group of patients with neurological disease, and is strengthened by its unique multidirectional version of the self-illuminated rod. Among a plethora of papers examining roll, it provides novel analysis of some neuro-anatomical correlations with deviations in subjective pitch, and offers a satisfying geometrical model explaining its finding of an association between deviations in pitch and roll in patients with OTR. It is therefore enlightening from a neurophysiological perspective, but perhaps more importantly, suggests that the examination of deviations in subjective pitch could be used not only as a means to detect brainstem disease in patients with vertigo or ataxia, but perhaps to hone in on a more specific localization.

Its weakness lies in the relatively small numbers of patients in each clinical group, so that directional correlations, when present, need to be confirmed. Furthermore, the neuro-anatomical categories were fairly gross (midbrain, pons, etc.) while, in reality, finer subdivisions likely would yield stronger conclusions. Further research with larger numbers of patients and with higher resolu-

tion imaging techniques, might help confirm and expand proposed associations. Finally, the technique does not analyze deviations in yaw (around the axis of the body), which previously have been associated with peripheral vestibular lesions. Combining the present method with a simple pointing test aimed at detecting such deviations in yaw would yield a more truly 3D picture of pathological perception of position in space in patients suffering from brainstem disease. ■

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

- 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

49. The rationale of mitoxantrone to treat NMO is based upon which potential mechanism?

a. Selective depletion of T lymphocytes
b. Reduction of relapse rate in patients with MS
c. Reduction of inflammatory lesions on MRI in MS patients
d. Selective depletion of B lymphocytes
e. Generalized immunosuppression

50. Which statement is *true*?

a. Generalized myasthenia is best treated with thymectomy alone.
b. Generalized myasthenia is best treated with steroids alone.
c. Generalized myasthenia responds best to a single plasma exchange, followed by 1 g intravenous methylprednisolone immediately.
d. Generalized myasthenia responds best to by low-dose oral corticosteroids.
e. None of the above are true.

51. Which of the following is *true* about the applause sign in neurodegenerative disorders?

a. It is a nonspecific sign of frontal lobe dysfunction.
b. It exclusively occurs in basal ganglia disorders.
c. It is a specific marker for Alzheimer's disease.
d. It is a specific marker for progressive supranuclear palsy.

52. All of the following are true about vitamin D *except*:

a. Light exposure is needed for endogenous vitamin D synthesis.
b. Vitamin D reduces oxidative stress.
c. Patients with severe vitamin D deficiency have more rapid cognitive decline.
d. Vitamin D supplements can cure dementia.
e. Vitamin D enhances natural immune function.

53. Distortions in the perception of the visual vertical dimension occurs in brainstem disease.

a. True
b. False

54. Elevated blood pressure upon admission with ischemic stroke increases the risk of death or neurologic deterioration.

a. True
b. False

55. Statins are proven safe to use after a patient sustains an intracerebral hemorrhage.

a. True
b. False

56. New York State-designated stroke centers are reporting lower mortality after acute ischemic stroke.

a. True
b. False

Answers: 49. d, 50. e, 51. a, 52. d, 53. a, 54. a, 55. b, 56. a.

In Future Issues: **Therapeutic Hypothermia**

Clinical Briefs in
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The essential monthly primary care update
By Louis Kuritzky, MD
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Spironolactone may save the day with resistant hypertension

Source: Engbaek M, et al. The effect of low-dose spironolactone on resistant hypertension. *J Am Soc Hypertens* 2010;4: 290-294.

Although the definition of resistant hypertension (r-HTN) has some variation, in the United States it is most commonly defined as inability to achieve target blood pressure with optimized doses of three antihypertensive agents, including a diuretic. Depending upon the population studied, as many as 15%-18% of subjects entering clinical trials — who presumably receive some of the best care medicine has to offer — are ultimately determined to have r-HTN.

Spironolactone (SPIR) is an aldosterone antagonist with modest diuretic activity. It has been shown to be effective in reducing blood pressure independent of aldosterone status; that is, one does not have to be a "high aldosterone" subject to enjoy meaningful BP reduction.

Engbaek et al report on 344 r-HTN subjects (mean BP 169/88, while already on three other medication), who were treated with SPIR 25 mg or 50 mg QD. They found a prompt and sustained mean BP reduction with SPIR: a 17/7 mm Hg reduction at 1 month, 24/10 mm Hg reduction at 3 months, and 26/11 mm Hg reduction at 6 months, all of which were statistically significant. The two most predictable adverse effects of SPIR, hyperkalemia and gynecomastia, were infrequent: 4.1% and 5.2%, respectively. Other clinical trials corroborate the utility and tolerability of SPIR to manage r-HTN. Clinicians should be reassured that < 10% of participants discontinued SPIR secondary to adverse events. ■

Fish oils: Where's the beef?

Source: Kromhout D, et al. n-3 fatty acids and cardiovascular events after myocardial infarction. *N Engl J Med* 2010;363: 2015-2026.

Observational data indicate that populations with high intake of fish oil have less cardiovascular disease (CVD) endpoints, spurring clinical trials to elucidate the relationship. A 2008 meta-analysis suggested that in persons with existing coronary heart disease (CHD), supplements of fish oils (n-3-fatty acids, e.g., eicosapentaenoic acid and docosahexaenoic acid) reduced CHD mortality by as much as 20%. This beneficial effect has been attributed to a reduced vulnerability to arrhythmia provided by fish oils; disappointingly, the inclusion of fish oil supplements in study subjects with implantable cardioverter-defibrillators did not confirm an anti-arrhythmic effect.

To clarify the potential role of fish oil supplementation for CHD patients, the Alpha Omega Trial enrolled men and women age 60-80 with a history of myocardial infarction (n = 4837). Study subjects were randomized to fish oil supplementation or placebo for 40 months.

Fish oil supplementation did not provide a statistically significant reduction in CVD events. Because many of the study subjects were receiving other interventions to reduce CVD risk (e.g., statins, antiplatelet agents, BP drugs), the authors posit that it is possible that these results, which are divergent from earlier trials, reflect the lesser available margin for improvement in persons already receiving other good tools for CVD risk reduction. ■

Gait speed and survival in older adults

Source: Studenski S, et al. Gait speed and survival in older adults. *JAMA* 2011;305:50-58.

The frailty of senior citizens is often portrayed on-stage by slow, stiff gait. This representation may be much more than theatre. Indeed, according to this pooled analysis of a very large data set (34,485 community-dwelling senior citizens), gait speed is linearly associated with mortality among persons age 65 years and older.

Gait speed in the studies was calculated by timing the study subjects while they walked distances varying from 2.4 to 6 meters by simply dividing the distance covered by elapsed time, recorded as meters/second. After obtaining baseline gait speed, study subjects were followed for 6-21 years.

For each 0.1 meter/second increase in baseline gait speed, there was a 12% higher rate of survival. This was independent of gender, BMI, smoking, blood pressure, or self-reported health.

Should clinicians wish to consider using gait speed as a health predictor, the method is simple: The patient is asked to walk over a predetermined distance with the instructions "Walk at your usual pace, as if you were walking down the street."

No particular encouragement or stimulus to promote intensification of effort is necessary. ■

Rifaximin for IBS without constipation

Source: Pimentel M, et al. Rifaximin therapy for patients with irritable bowel syndrome without constipation. *N Engl J Med* 2011;364:22-32.

It has been recognized for more than a decade that most patients with IBS have abnormal lactulose hydrogen breath tests results, consistent with small bowel bacterial overgrowth. Neomycin treatment, which can re-establish bowel flora, has shown modest efficacy in IBS, but is limited by tolerability issues. Other systemic antibiotics have not provided consistent symptomatic improvement in IBS. A previous pilot trial of rifaximin found that 10 days of treatment provided symptomatic improvement as measured 10 weeks later.

The TARGET trials are two identical double-blind, placebo-controlled trials of subjects with IBS without constipation. Patients were randomly assigned to rifaximin 550 TID or placebo for 2 weeks. Symptoms were monitored for up to 10 weeks. The primary outcome was the proportion of individuals reporting adequate relief of global IBS symptoms. The main secondary outcome was relief of bloating. Additional outcomes included abdominal pain and stool consistency.

Rifaximin provided a statistically significant improvement in global symptoms, bloating, abdominal pain, and stool consistency. Consonant with a very favorable tolerability profile seen in prior clinical trials, the safety profile of rifaximin was similar to placebo in this report. It is anticipated that systemic effects of rifaximin will be rare, since only a miniscule proportion of administered drug enters the systemic circulation.

Short-term treatment with rifaximin can provide statistically significant improvements for patients with IBS without constipation. ■

Pre-exposure HIV prophylaxis for men who have sex with men

Source: Grant RM, et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. *N Engl J Med* 2010;363:2587-2599.

Men who have sex with men (MSM) are a high-risk group for acquisition of HIV, but other than safe sex practices, there has been little encouraging information about chemoprophylaxis. Certainly clinicians have some degree of confidence in the efficacy of post-exposure HIV prophylaxis post-needle stick in the health care setting, but the only population in which pre-exposure prophylaxis has been studied utilized tenofovir vaginal gel in women in Africa, reporting a 39% reduction in HIV infection.

HIV-seronegative men (or transgender women) who have sex with men (n = 2499) were randomized to a combination antiretroviral treatment (emtricitabine and tenofovir) or placebo once daily. They were followed for up to 2.8 years (median 1.2 years).

During follow-up, all subjects were seen every 4 weeks, during which they were counseled on safe sex practices, sexually transmitted diseases (STDs), and STD risk reduction.

At the conclusion of the trial, 36 of 1224 pre-exposure prophylaxis patients sero-converted vs 64 of 1217 placebo subjects (a 44% reduction in HIV incidence). Tolerability of the active antiviral treatment was excellent. The risk reduction demonstrated in this trial seems all the more remarkable because the reduction in unsafe sex practices attributed to the repetitive sexual health education and counseling during the trial would tend to minimize benefits of the medication. ■

Treating venous thromboembolism with rivaroxaban

Source: The EINSTEIN Investigators. Oral rivaroxaban for symptomatic venous thromboembolism. *N Engl J Med* 2010;363:2499-2510.

The treatment of acute venous thromboembolism commonly is managed successfully with enoxaparin followed by intermediate to long-term prevention of recurrent thromboembolism with warfarin.

Despite a proven track record of efficacy, warfarin has limitations, including the need for ongoing monitoring, problematic interactions with medications and food, and risk of significant bleeding, which occurs in 1%-2% of patients using long-term warfarin.

Rivaroxaban is a direct factor X inhibitor administered orally once daily. It is effective both acutely (hence, it may be utilized instead of heparin during the acute phase of venous thromboembolism) and chronically. Because it does not have any interactions with food and does not require monitoring, it provides many fewer obstacles to successful patient management than warfarin or heparin-warfarin combinations.

The EINSTEIN Investigators reported on two trials: One compared rivaroxaban with enoxaparin + warfarin for acute venous thromboembolism (n = 3449), and the other compared rivaroxaban with placebo in subjects who had completed 6 months of warfarin treatment for DVT.

For acute venous thromboembolism, rivaroxaban was non-inferior to enoxaparin + warfarin. In the long-term trial, rivaroxaban was superior to placebo. Rivaroxaban appears to provide an attractive alternative treatment for venous thromboembolism. ■

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Escitalopram for Menopausal Hot Flashes

In this issue: Escitalopram for menopausal hot flashes, rifaximin for IBS without constipation, herpes zoster vaccination, antiepileptics drugs and fracture risk, and FDA Actions.

Escitalopram for hot flashes

Since the Women's Health Initiative was published in 2003, the use of hormone therapy for the treatment of postmenopausal hot flashes has dropped dramatically. Both selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) have been studied to relieve postmenopausal symptoms, but no agent has been conclusively shown to be effective. A new study suggests that escitalopram (Lexapro™) may offer some relief.

In a study recently published in the *Journal of the American Medical Association*, 205 menopausal women were randomized to 10-20 mg per day of escitalopram or matching placebo for 8 weeks. The primary outcome was the frequency and severity of hot flashes with the average hot flash frequency at nearly 10 per day at baseline. Escitalopram resulted in 1.41 fewer hot flashes per day compared to placebo ($P < 0.001$), although both the active drug group and placebo groups noted reductions. Escitalopram also reduced hot flash severity. There was no difference among women of different races, and the discontinuation rate was small. The authors concluded that escitalopram 10-20 mg per day compared with placebo resulted in fewer and less severe menopausal hot flashes at 8 weeks (*JAMA* 2011;305:267-274). Whether the same effect can be expected with racemic citalopram (Celexa™) is unknown. ■

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Rifaximin for IBS without constipation

Rifaximin, an oral, nonsystemic (poorly absorbed) broad-spectrum antibiotic, may help relieve symptoms of irritable bowel syndrome according to two identically designed studies published in the *New England Journal of Medicine*. A total of 1060 patients who had IBS without constipation were randomized to rifaximin 550 mg three times daily for 2 weeks or matching placebo. The primary endpoint was a proportion of patients with adequate relief of global IBS symptoms; the secondary endpoint was relief of bloating. Significantly more patients in the rifaximin group had adequate relief of IBS symptoms during the first 4 weeks of treatment (40.7% vs 31.7%; $P < 0.001$), as well as improvement in bloating (40.2% vs 30.3%; $P < 0.001$). The incidence of adverse events was similar in the two groups. The authors concluded that among patients who had IBS without constipation, treatment with rifaximin for 2 weeks provided significant relief of the IBS symptoms of bloating, abdominal pain, and loose or watery stools (*N Engl J Med* 2011;364:22-32).

An accompanying editorial points out that the benefit from rifaximin was sustained over 10 weeks after a short 2-week treatment course, but also points out that benefit of the drug was a mere 9%-12% improvement over placebo, barely clinically relevant. Still, for patients who have IBS without constipation who have not responded to other therapies, a single treatment

cycle could be tried (*N Engl J Med* 2011;364: 81-82). ■

Herpes zoster vaccination rates and incidence of shingles

The herpes zoster vaccine cuts the rate of shingles by 55% in the elderly population according to a new report in the *Journal of the American Medical Association*. Researchers at Kaiser Permanente in Southern California performed a retrospective cohort study of health plan members, 75,000 of whom were vaccinated against shingles (age 60 and older) and 225,000 age-matched controls who did not receive vaccine. The rate of herpes zoster was 6.4/1000 person-years in the vaccinated group and 13.0/1000 person-years in the unvaccinated group (hazard ratio, 0.45; 95% confidence interval, 0.42-0.48). Reduction in herpes zoster occurred in all age groups and among individuals with chronic disease. The rate of ophthalmic herpes zoster and hospitalizations for herpes zoster were also significantly reduced.

The authors of the study concluded that among immunocompetent community-dwelling adults age 60 and older, receipt of the herpes zoster vaccine was associated with a lower incidence of herpes zoster (*JAMA* 2011;305:160-166). The study is important because only 10% of those aged 60 and older received the shingles vaccine in 2009, whereas nearly one of three people in the United States will develop shingles in their lifetime. ■

Fracture risk with antiepileptic drugs

Most antiepileptic drugs (AEDs) are associated with an increased risk of nontraumatic fracture according to a retrospective match cohort study. Nearly 16,000 patients with a history of prior AED use (carphenazine, clonazepam, ethosuximide, felbamate, gabapentin, lamotrogine, levetiracetam, oxcarbazepine, phenobarbital, phenytoin, pregabalin, primidone, topiramate, valproic acid, or vigabatrin) were compared to up to three matched controls each. Rates of fractures of the wrist, hip, and vertebrae were measured between 1996 and 2004. A significant increase in fracture risk was found for most AEDs, with an adjusted odds ratio of 1.24 for clonazepam to 1.91 for phenytoin. The only AED not associated with increased fracture risk was valproic acid.

The authors concluded that most AEDs are associated with an increased risk of nontraumatic fractures in individuals age 50 or older. They suggested that the risk of fracture with newer AEDs needs to be determined, as well as the effect of bone protective medications in this population (*Arch Neurol* 2011;68:107-112). The mechanism of increased fracture risk in patients using AEDs is unknown, but may be related to accelerated vitamin D catabolism, calcium absorption, or an effect on osteoblasts. ■

FDA Actions

The FDA has approved vilazodone hydrochloride for the treatment of depression in adults. The drug is a selective serotonin reuptake inhibitor as well as a partial agonist of the 5HT 1a receptor. The drug was approved in dosages of 10 mg, 20 mg, and 40 mg for major depressive disorder or major depression. Vilazodone is touted as having fewer sexual side effects than other antidepressants. It carries the same boxed warning as other antidepressant regarding suicidal thinking and behavior in children, adolescents, and young adults. Vilazodone will be marketed by Clinical Data Inc. as Viibryd™.

The FDA is limiting the amount of acetaminophen in combination prescription pain medications. The new requirement limits the amount of acetaminophen to 325 mg in each tablet or capsule. Common medications that will be affected include codeine (acetaminophen with codeine), oxycodone (Percocet®), and hydrocodone (Vicodin®). Over-the-counter acetaminophen products are not affected. This action is being taken to limit acetaminophen-related liver failure. It is felt that lowering the amount of acetaminophen in these products will have minimal effect on efficacy for treating pain. The change will be phased in over 3 years.

The FDA has approved a new transmucosal form of fentanyl for the treatment of breakthrough pain for adults with cancer. The drug is indicated for the management of breakthrough pain in patients with cancer ages 18 and older, who use opiate pain medication around the clock. Breakthrough pain is defined as pain that comes on suddenly for short periods of time and is not alleviated by the patient's normal pain management plan. Patients must be opioid-tolerant to qualify for use with transmucosal fentanyl. The drug is available only through a Risk Evaluation and Mitigation Strategy (REMS) program, which is intended to minimize risk of misuse, abuse, addiction, and overdose. Fentanyl sublingual tablets are available as 100 mcg, 200 mcg, 300 mcg, 400 mcg, 600 mcg, and 800 mcg strengths. Fentanyl sublingual tablets are marketed by ProStrakan Inc. under the trade name Abstral®. ■