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INSIDE

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First Successful Surgical Trial for Gene Therapy in Parkinson's Disease

ABSTRACT & COMMENTARY

By Claire Henchcliffe, MD

Associate Professor of Neurology and Neuroscience, Weill Cornell Medical Center

Dr. Henchcliffe reports she is on the speakers bureau and advisory board for Allergan and Teva; speakers bureau for Boehringer-Ingelheim, GlaxoSmithKline, and Novartis; advisory board for Merz; and is a consultant for Gerson Lehman Group and Guidepoint Global.

Synopsis: *A controlled surgical trial of glutamic acid decarboxylase gene therapy, targeting the subthalamic nucleus in advanced Parkinsons's disease, demonstrated statistically significant improvement in motor symptoms off medication in those receiving gene therapy compared with controls.*

Source: LeWitt PA, et al. AAV2-GAD gene therapy for advanced Parkinson's disease: A double-blind, sham-surgery controlled, randomised trial. *Lancet Neurol* 2011;10:309-319.

THIS MULTICENTER, DOUBLE-BLIND, RANDOMIZED, SHAM-SURGERY CONtrolled trial examined the effects of introducing the glutamic acid decarboxylase (GAD) gene into the subthalamic nucleus (STN), bilaterally, of 45 individuals with advanced Parkinson's disease (PD), by means of the adeno-associated viral vector 2 (AAV2). This approach has well-described scientific underpinnings. GAD catalyzes the rate-limiting step in GABA synthesis, so by increasing GABA-ergic "tone," it would "convert" STN output from the abnormally excitatory state seen in PD, thus alleviating motor symptoms. In the present study, participants were randomized to one of two scenarios: 1) AAV-GAD infusion or 2) sham surgery. Mean participant age was 61.8 ± 7 and 60.6 ± 7.4 years (AAV-GAD and sham groups, respectively), and mean disease duration was 10.6 ± 4.3 years and 12.0 ± 5 years (AAV-GAD and sham groups, respectively). Of the 22 subjects assigned to receive AAV-GAD, 16 were eligible for analysis, and 21/23 subjects assigned to sham-surgery were eligible (exclusions were based on improper targeting revealed by subsequent imaging, infusion failure, pump malfunction). Over a 6-month duration, investigators were encouraged to keep medications stable. Notably, at this time point, Uni-

fied Parkinson's Disease Rating Scale (UPDRS) motor subscores, with patients in the "off" state, improved from 34.8 ± 1.6 to 26.6 ± 2.0 in the AAV-GAD group, compared with 39.0 ± 1.9 to 34.3 ± 2.5 in the sham-surgery group ($P = 0.04$). In a responder analysis of these same scores (cutoff: 9 point improvement), 50% in the AAV-GAD group were assessed as responders, compared with just 14.3% in the sham surgery group ($P = 0.03$). Changes in wearing off response and freezing of gait also were superior in the AAV-GAD group vs the sham-surgery group.

■ COMMENTARY

The investigators have designed an exceedingly rigorous approach to test effects of somatic gene therapy in advanced PD, following a previous open-label trial of unilateral GAD-AAV gene that demonstrated safety and tolerability. Surgical introduction of the GAD gene into the bilateral STN resulted in achievement of the study's primary endpoint, that is, a significant improvement in UPDRS motor scores (off medication) over the sham-surgery "placebo." This is encouraging and provides hope for a gene therapy intervention to provide an efficacious and safe treatment for PD. There are a number of features in the study's design that likely contributed to its success. First, patients were selected on rigorous clinical criteria (including PD diagnosis of > 5 years and a sustained levodopa response of > 12 months) plus a requirement that 18F-flurodeoxyglucose positron emission tomography imaging was consistent with a diagnosis of PD according to published criteria. This actually resulted in 11 screening failures, quite surprising in a highly selected population. Second, the investigators chose an elaborately simulated sham-surgery procedure, with OR personnel making extensive efforts to reproduce all features of the AAV-GAD infusion, including stereotactic frame placement, sounds of microelectrode recordings played during the sham procedure, similar external catheter and pump arrangements, and a similar time frame for the procedure. Subjects were asked to guess assignment on post-operative day 3, and in both groups the majority thought they had undergone AAV-GAD infusion rather than sham-surgery. Third, the investigators examined results separately from subjects whose catheter tip placement (therefore gene transfer) was inaccurate, and 4/5 of these subjects had no improvement during the study. In summary, the methodology employed will provide insight for trials to come, and it will be fascinating to see more long-term data from this first successful sham-surgery controlled gene therapy trial. ■

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Early Prediction of Long-Term Outcome After Traumatic Spinal Cord Injury

ABSTRACT & COMMENTARY

By John J. Caronna, MD

Professor of Clinical Neurology, Weill Cornell Medical College

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

Synopsis: *A composite score that combines age, motor power, and light touch perception can predict recovery of walking with great accuracy in patients with traumatic spinal cord injury.*

Source: van Middendorp JJ, et al. A clinical prediction rule for ambulation outcomes after traumatic spinal cord injury: A longitudinal cohort study. *Lancet* 2011;377:1004-1010.

A PRECISE KNOWLEDGE OF THE PROGNOSIS FOR RECOVERY OF walking after traumatic spinal cord injury (TSCI) is of extreme importance, not only to the injured individual but also to the treating physician, who must consider acute surgical and pharmacologic interventions, and afterwards, set realistic goals for rehabilitation. To satisfy this clinical need, van Middendorp and associates propose a clinical prediction rule to assess a patient's chances of walking independently after TSCI. The rule was derived from the American Spinal Injury Association/International Spinal Cord Society Neurological Standard Scale.[1]

The study population comprised 1442 adults with TSCI admitted to 19 European centers between 2001 and 2008. Because no proven effective treatment of TSCI is avail-

TABLE. Clinical Prediction Rule Variables

	Range of Scores	Weighted Coefficient	Minimum Score	Maximum Score
Age >/= 65 years	0-1	-10	-10	0
Motor Score (L3)	0-5	2	0	10
Motor Score (S1)	0-5	2	0	10
Light Touch Score (L3)	0-2	5	0	10
Light Touch Score (S1)	0-2	5	0	10
Total			**-10**	**40**

Adapted from: van Middendorp JJ, et al. A clinical prediction rule for ambulation outcomes after traumatic spinal cord injury: A longitudinal cohort study. *Lancet* 2011;377:1004-1010.

able, no attempt was made to standardize or record the details of the treatments applied and the focus or intensity of the rehabilitation programs prescribed.

Enrolled patients underwent early (< 15 days) and late (1-year follow up) clinical examinations. Of these, 492 had available outcome measures. The ability to walk independently 1 year after injury was the primary functional outcome. Six-month follow-up measurements were used for patients without 1-year follow-up examination. Spinal cord independence measures[2] were assessed by physicians, physiotherapists, and occupational therapists.

The variables showing excellent discrimination between independent walkers and dependent or non-walkers were: age (< 65 vs ≥ 65 years), motor scores of the quadriceps femoris (L3, L4) and gastrocsoleus (S1) muscles, and light touch sensation of dermatomes L3 and S1. The performance of the clinical prediction rule was validated in an additional 389 adults with TSC1 admitted between 2008 and 2009. The probability that an individual would be able to walk at 1 year after TSCI was estimated using the weighted coefficients of the final prediction rule (*see Table*) with a minimum total score of -10 and a maximum total score of 40.

The authors calculated the probability and 95% confidence interval of walking independently at 1 year, based on the prediction rule score: A score of -10 predicts no chance of independent ambulation. At a score of 10, the probability is approximately 35%, at 15 it is about 77%, at 20 it is almost 90%, and at a score of 30 or above, the probability is 100%.

■ COMMENTARY

Prior to the widespread recognition of the value of multivariate prognostic models to determine functional outcome after traumatic brain injury or following medical (non-traumatic) coma, physicians often based early prognostications on a single neurological sign. In the case of coma, the most common predictor was the presence or absence of the pupillary light reflex. In spinal cord injury, the predictor usually chosen was the presence or absence of anal sensation.

The authors have used logistic regression analysis to develop a simple clinical prediction rule to calculate the probability of a patient being able to walk independently at 1 year after TSCI. On the basis of age and four clinical neurologic tests, the probability of walking can be calculated more easily and probably more accurately than with the grading systems in use at present. The authors, however, have not provided detailed information about the quality of walking in their good outcome patients. Such information is necessary to determine whether a novel treatment strategy results in a better than predicted, that is, improved outcome in patients with prediction rule scores in the intermediate range of 10 to 20.

Other investigators will no doubt also wish to determine whether the combined use of the prediction rule with somatosensory evoked potentials improves prognostic accuracy. Nevertheless, the authors have provided clinicians with a validated, simple, clinical prediction rule that can be used to counsel TSCI patients and their families during the initial phase after injury. ■

References

1. American Spinal Injury Association. International standards for neurological classification of spinal cord injury, revised 2002. Chicago IL: Amer Spinal Injury Assoc; 2002.
2. Catz A, et al. A multicenter international study on the Spinal Cord Independence Measure, version III: Rasch psychometric validation. *Spinal Cord* 2007;45:275-291.

Flu Shots and Myasthenia Gravis

ABSRACT & 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: *Seasonal flu and H1N1 vaccines are safe for patients with myasthenia gravis and should be administered.*

Source: Auriel E, et al. Safety of influenza and H1N1 vaccinations in patients with myasthenia gravis, and patient compliance. *Muscle Nerve* 2011;43:May. Accepted manuscript online: 25 FEB 2011DOI: 10.1002/mus.22077.

IS IT SAFE TO VACCINATE MYASTHENIA GRAVIS PATIENTS AGAINST the flu, or is there a tangible risk of myasthenic worsening? During the winter of 2009-10, the Ministry of Health

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*

Rotational Vertebral Artery Syndrome: A Vascular Cause of Isolated Vertigo

Source: Noh Y, et al. Rotational vertebral artery syndrome due to compression of nondominant vertebral artery terminating in posterior inferior cerebellar artery. *J Neurol* 2011; Online DOI 10.1007/s00415-011-6005-1.

ROTATIONAL VERTEBRAL ARTERY SYNDROME (RVAS) IS A rare syndrome usually caused by compression of the dominant vertebral artery in the neck with extreme head rotation to the contralateral side. Most symptomatic patients have stenosis or hypoplasia of one vertebral artery. At the same time that vertigo occurs, there is usually nystagmus, with the direction of the fast phase on the same side as the compressed vertebral artery. The authors described a patient with a hypoplastic vertebral artery that ended in the posterior inferior cerebellar artery with symptoms occurring during head turn in the direction opposite the hypoplastic artery. This example suggests that ischemia of the inferior cerebellum or lateral medulla explains the symptoms and signs of RVAS. ■

Stroke Outcome Prediction After Middle Cerebral Artery Territory Infarction

Source: Vora NA, et al. A 5-item scale to predict stroke outcome after cortical middle cerebral artery territory infarction. Validation from results of the Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution (DEFUSE) study. *Stroke* 2011;42:645-649.

THE AUTHORS RETROSPECTIVELY REVIEWED 129 PATIENTS over a 2-year period and considered clinical, laboratory, and imaging parameters as potential predictors of outcome. Inclusion criteria were unilateral hemispheric infarcts within the middle cerebral artery territory. The primary outcome measure was favorable recovery, as defined by modified Rankin Score < 2 at 30 days. A multivariable model was used to develop a five-item scale to predict stroke recovery.

Continued on page 69

of the Israeli government recommended that citizens with chronic conditions be vaccinated against both H1N1 and seasonal influenza virus. A subgroup of patients with myasthenia within this population served as the nucleus for this analysis.

Among 74 patients with myasthenia gravis followed in outpatient neuroimmunology clinics at Sourasky Medical Center and Sheba Medical Center in Tel Aviv, Israel, patient questionnaires were completed during a clinic visit or telephone interview to determine whether they had received either the seasonal influenza or H1N1 vaccine, or both during the winter of 2009-10. If no vaccination was received, the patient was asked to explain why, and, if vaccination was performed, information was obtained regarding adverse effects, particularly worsening of myasthenia.

Seasonal influenza flu vaccination was given to 38 myasthenia patients (51.4%) and H1N1 vaccine to 24 (32.4%), with 20 patients (27%) receiving both. No adverse events occurred among those who underwent seasonal influenza flu vaccination, but following H1N1 vaccine, three patients experienced adverse effects, one each with facial palsy (six weeks following vaccination), acute bronchitis (a few days after vaccination), and fever. No patient in either group reported worsening of myasthenia. Among those who declined vaccination, fear of adverse effects was cited most often, including myasthenic (31.5%) and non-myasthenic concerns (42.6%), with 14.8% (n = 8) being advised by their physician to abstain from the program. Seasonal influenza flu and H1N1 vaccination appears to be safe for patients with myasthenia.

■ COMMENTARY

Vaccines may be composed of whole killed organisms, live attenuated virus, components of the organism or their denatured toxin, or may be created as a conjugate vaccine by covalently attaching a polysaccharide antigen to a protein carrier. The last, which includes those for *Haemophilus influenzae*, *Streptococcus pneumoniae*, and *Neisseria meningitidis*, cannot produce the natural disease but provokes an immune response that is directed against the antigen and hence is protective against the disease. Neurological complications post-vaccination, although rare, are among the most serious, and, although a causal relation may be difficult to prove, include encephalitis, meningitis, Parkinsonism, seizures, stroke, transverse myelitis, and Guillain-Barre syndrome. Neurological complications have been reported following a host of vaccines, including measles-rubella, varicella, influenza, hepatitis

Stroke Alert (continued)

Five independent predictors of outcome were: age (odds ratio [OR] = 1.09, $P = 0.001$), NIH Stroke Scale (OR = 1.17, $P = 0.003$), infarct volume (OR=1.01, $P = 0.03$), admission white blood cell count (OR = 1.16, $P = 0.04$), and presence of hyperglycemia (OR = 4.2, $P = 0.04$). Combining these variables into a point scale improved their prediction value, and when applied to the DEFUSE study population for validation, achieved a sensitivity of 83% and specificity of 86%. ■

Lowering Blood Pressure Reduces Hematoma Growth After Acute Intracerebral Hemorrhage

Source: Arima H, et al, for the Intensive Blood Pressure Reduction in Acute Cerebral hemorrhage Trial (INTERACT) Investigators. Lower treatment blood pressure is associated with greatest reduction in hematoma growth after acute intracerebral hemorrhage. *Hypertension* 2010;56:852-858.

INTERACT INCLUDED 404 PATIENTS WITH ACUTE INTRACEREbral hemorrhage (ICH), elevated systolic blood pressure (BP) (150 to 220 mmHg), and capacity to lower BP within 6 hours of onset. CT was performed at baseline and at 24 hours to compare hematoma size. There was no significant association between baseline systolic BP levels and hematoma volume. Maximum reduction in hematoma growth occurred in the one-third of patients with the lowest on-treatment systolic BP levels (median = 135 mmHg). Intensive BP reduction to systolic levels between 130 and 140 mmHg is likely to provide maximum protection against hematoma growth. ■

Dementia Occurs in Approximately 20% of Patients After a First Stroke

Source: Bejot Y, et al. Prevalence of early dementia after first-ever stroke. A 24-year population-based study. *Stroke* 2011;42:607-612.

FROM 1985 TO 2008, ALL FIRST-EVER STROKES IN THE CITY OF Dijon, France (150,000 inhabitants) were recorded, and among those patients who were testable (3201/3948 or 81%), 20.4% had post-stroke dementia. The prevalence of post-stroke dementia in patients with lacunar disease was 7 times higher than in patients with intracerebral hemorrhage. Age, vascular risk factors, presence of hemiplegia, and use of prestroke antiplatelet medications were associated with an increased prevalence of post-stroke dementia. ■

A and B, rabies, meningococcal, pneumococcal, *H. flu*, and diphtheria–tetanus–pertussis.[1] Among patients with immune-mediated disease, stimulating the immune system by vaccination raises the concern that the underlying disease will be similarly incited. Risk of developing the disease must be weighed against risk of vaccination. For myasthenics, seasonal influenza flu and H1N1 vaccination appears to be safe. ■

Reference

1. Miravalle A, et al. Neurological complications following vaccinations. *Neurol Res* 2010;32:285-292.

Decompressive Craniectomy for Severe Diffuse TBI

ABSTRACT & COMMENTARY

By Halinder S. Mangat, MD

Assistant Professor of Clinical Neurology, Weill Cornell Medical College

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

Synopsis: *Decompressive craniectomy for severe diffuse traumatic brain injury and refractory intracranial hypertension (ICP) reduces ICP but increases unfavorable outcomes.*

Sources: Cooper DJ, et al for the DECRA Trial Investigators and the Australian and New Zealand Intensive Care Society Clinical Trials Group. Decompressive craniectomy in diffuse traumatic brain injury. *N Engl J Med* 2011. DOI: 10.1056/NEJMoa1102077. Servadei F. Clinical value of decompressive craniectomy. *New Engl J Med* 2011. DOI: 10.1056/nejme1102998.

DECOMPRESSIVE CRANIECTOMY IS COMMONLY USED IN THE treatment of refractory intracranial hypertension following malignant middle cerebral artery infarction (MCAI), traumatic brain injury (TBI), and occasionally, aneurysmal subarachnoid hemorrhage (SAH). The beneficial effects of early decompressive craniectomy in improving outcomes and reducing mortality has been demonstrated in malignant MCAI.[1,2] However, prior to the DECRA trial, no large, randomized clinical trial was completed to study its role in refractory intracranial hypertension following severe TBI.

In this study, the investigators evaluated early (in the first 72 hours) bifrontotemporoparietal craniectomy in the

management of refractory intracranial hypertension following diffuse brain injury. Refractory ICP was defined as ICP more than 20 mmHg for more than 15 minutes during any 1 hour. All patients received tier 1 therapies, which included hypertonic saline, mannitol, optimal sedation, neuromuscular paralysis, and CSF diversion. After this stage, patients were randomized to either surgery or tier 2 therapies, which included hypothermia and barbiturates. The investigators screened 3478 patients between the ages of 15 and 59 over 7 years, during which time 155 were enrolled. Patients with GCS between 3 and 8 were included. Exclusions were based on dilated and unreactive pupils, mass lesions requiring surgical intervention, spinal cord injury, and cardiac arrest at scene.

The results show a worse outcome for patients who underwent craniectomy. Unfavorable outcome was 70% in these patients vs. 50% in patients who received standard therapies. While deaths were not higher, more patients had worse functional outcomes after surgery. Surgery, however, lowered ICP, time spent above ICP of 20 mmHg, and improved cerebral perfusion pressure (CPP). It also decreased mechanical ventilation days and days in ICU, but not days in hospital.

■ COMMENTARY

This trial examines early craniectomy with a lower threshold for definition of intractable intracranial hypertension. The results have been eagerly anticipated and the findings are unexpected. However, it is to be noted that the study tested the benefit of craniectomy in a very small subgroup of severe TBI patients. Only patients with diffuse head injury were included. Patients with mass lesions who comprise a large subgroup of severe head injury patients and frequently require surgical intervention were excluded. The investigators screened 3478 patients and only 155 were eligible for enrollment (4.4%). This is further evidence that this study looked at a small, highly selected subgroup of patients with severe TBI.

Another confounder is the significantly larger percentage of patients in the craniectomy group with bilateral unreactive pupils. Such patients tend to do poorly in spite of all therapies. When correcting for this, the negative effect of craniectomy on outcome disappeared.

Bifrontotemporoparietal craniectomy is a radical procedure. Its effect on cerebral blood flow and metabolism may be detrimental[3,4] or beneficial.[5] There is the possibility of irreversible metabolic injury in spite of reduction in ICP.[4] Decreases in ICP can cause hyperperfusion due to higher CPP and poor autoregulation worsened by decompression.

The study concludes that early craniectomy is not beneficial in treating diffuse head injury. However, as discussed in the accompanying editorial, this should not lead to the abandonment of the surgical procedure until data from other trials are available. We should be circumspect in performing radical craniectomy surgery in diffuse TBI.

The RESCUEicp trial,[6] which is still enrolling patients, is studying the effect of last-stage randomization to decompressive craniectomy vs barbiturate coma in refractory intracranial hypertension. This will elucidate the effect of late craniectomy. The trial does not limit enrollment by the underlying nature of brain injury or the type of surgery performed for decompression — bifrontal, unilateral, or bilateral — and will be more inclusive. An area that still remains to be examined is the potential benefit of primary decompressive craniectomy frequently necessitated by large focal lesions, such as acute subdural hematomas. ■

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1. Vahedi K, et al. Sequential-design, multicenter, randomized, controlled trial of early decompressive craniectomy in malignant middle cerebral artery infarction (DECIMAL Trial). *Stroke* 2007;38:2506-2517.
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Genetic Susceptibility to Fatal Rash from Carbamazepine? The Case for HLA Screening

ABSTRACT & COMMENTARY

By Padmaja Kandula, MD

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

Synopsis: *Carbamazepine has been linked with severe forms of hypersensitivity reactions. As such, genome wide approaches to identify patients-at-risk have become increasingly important.*

Sources: Chen P, et al. Carbamazepine-induced toxic effects and HLA-B*1502 screening in Taiwan. *New Engl J Med* 2011;364:1126-1133. McCormack M, et al; HLA-A*3101 and carbamazepine-induced hypersensitivity reactions in Europeans. *New Engl J Med* 2011;364:1134-1143.

The most severe form of carbamazepine hypersensitivity reactions is Stevens-Johnson Syndrome (SJS), characterized by a blistering rash involving the mucous membranes and systemic inflammatory side effects. The most extreme form, toxic epidermal necrolysis (TEN), involves even greater epidermal detachment. Both syndromes carry a high risk of mortality and are the focus of two recent studies from Taiwan and the UK. Previous reports have confirmed the association of SJS and TEN with HLA-B*1502 allele in individuals of Han Chinese descent. In this first paper from Taiwan, the authors prospectively screened patients, by using HLA-B*1502 genotyping, to identify subjects at risk for SJS-TEN before starting clinical treatment with carbamazepine. The second paper from the UK presents data implicating the HLA variant, HLA-A*3101, in the full range of carbamazepine-associated hypersensitivity reactions.

Chen et al screened patients from 23 hospitals in Taiwan and identified 4877 subjects who were carbamazepine candidates (epilepsy, neuralgia, neuropathic pain, tinnitus, bipolar or psychiatric disorders). Patients with a previous history of carbamazepine allergy, bone marrow transplant, and non-Han Chinese descent were excluded. Patients were told to defer taking carbamazepine until results of genetic testing were complete. All individuals had an initial screening visit. Only HLA-B*1502 positive individuals were asked to return for a second office visit to communicate test results and offer alternative treatments. Weekly telephone interviews with all subjects were conducted over the next 2 months. Any clinical suspicion of adverse drug reaction prompted an immediate hospital evaluation by a staff dermatologist. Based on an 8% historical prevalence of the HLA-B*1502 allele in the Taiwanese population, the authors determined that 4419 subjects would render a power of 99% to detect a reduction in the historical incidence of carbamazepine-induced SJS-TEN from 0.25% to 0.03%.

In Taiwan, 4855 patients underwent genotyping; 7.7% (372) were found to be HLA-B*1502 positive and advised not to take carbamazepine and 215 were given alternative treatment (gabapentin, lamotrigine, naproxen, imipramine, or prednisolone). Among all 4855 subjects, 211 (4.3%) developed mild transient rash and pruritis and five were HLA-B*1502 positive. Seven patients had more severe cutaneous symptoms. Three patients had maculopapular eruption, two with hypersensitivity syndrome, and two patients were noted with urticaria. One patient with urticaria was HLA-B*1502 positive and had taken oxcarbazepine before study enrollment. No cases of SJS-TEN were noted in any subjects during the 2-month follow-up.

McCormack et al recruited subjects from either the Liverpool collaborators or the EPIGEN consortium. Subjects were divided into three categories: 1) hypersensitivity syndrome defined as the presence of rash or liver involvement within 3 months of initiation of carbamazepine treatment, accompanied by two of the following: prolonged recovery phase despite drug withdrawal, fever, or involvement of other internal organs (liver, kidney, lung, central nervous system, heart, muscle, thyroid, or lymphoid system); 2) maculopapular exanthema, defined as rash without systemic symptoms; and 3) SJS-TEN defined as skin detachment between 10-30% of body surface area with target skin lesions. Both population and clinical controls (those with epilepsy taking carbamazepine for 3 months or greater without clinical or biochemical hypersensitivity) were used. Single-nucleotide polymorphisms and imputation with high-resolution confirmation sequence-based HLA typing was performed to test for HLA allele association and clinical disease. Follow-up genotyping confirmed the HLA-A*3101 as a risk factor for the following: hypersensitivity syndrome with an odds ratio of 12.41 (27 subjects vs 257 controls without adverse drug reactions), maculopapular exanthema with an odds ratio of 8.33 (106 subjects vs 257 controls), and SJS-TEN with an odds ratio of 25.93 (12 subjects vs 257 controls). Overall, the presence of the HLA-A*3101 allele increased the risk of carbamazepine induced hypersensitivity reactions from 5% to 26%, whereas its absence reduced the risk from 5% to 3.8%.

■ COMMENTARY

Both of these papers contribute to the mounting evidence that various HLA alleles predispose select individuals to carbamazepine hypersensitivity reactions. As increased mortality is associated with the most severe of these reactions, SJS-TEN, prescreening individuals may be of increasing clinical importance, particularly in the case of the HLA-B*1502 allele and the associated risk reduction of SJS-TEN in Han Chinese. That said, the greatest criticism of both of these articles is the lack of definitive safety data regarding alternative treatment. It is unknown whether compounds structurally similar to carbamazepine carry similar hypersensitivity risks. In addition, further work will be needed to clarify whether other individuals of European and Asian descent carry the same risk for hypersensitivity reactions. ■

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 rceive a credit letter. When an evaluation form is received, a credit letter will be mailed to the participant.

CME Questions

62. A recent clinical trial examined effects of the glutamic acid decarboxylase (GAD) gene in Parkinson's disease (PD). Which statement correctly describes the rationale for this approach?

a. GAD gene expression in the subthalamic nucleus reduces PD-associated aberrant output from this nucleus resulting in improvement of motor symptoms.

b. The GAD gene is the rate-limiting step in glutamate synthesis; thus, gene transfer increases glutamate output from the subthalamic nucleus and improves motor symptoms.

c. GAD gene expression in the striatum reduces excitatory output seen in PD.

d. Dyskinesias associated with advanced PD are reduced by glutamate receptor antagonists.

63. Decompressive craniectomy has been used to treat intractable intracranial hypertension in:

a. traumatic brain injury.

b. ischemic stroke.

c. intracerebral hemorrhage.

d. subarachnoid hemorrhage.

e. All of the above

64. A traumatic spinal cord injury patient with a prediction rule score of 25 has a probability of independent ambulation at 1 year of:

a. 25%.

b. 33%.

c. 50%.

d. 75%.

e. 95%.

65. Which of the following statements is true?

a. Patients with myasthenia should not receive seasonal influenza flu vaccination.

b. Patients with myasthenia should not receive H1N1 flu vaccination.

c. Patients with myasthenia may safely receive seasonal influenza flu and H1N1 vaccination without fear of worsening myasthenia.

d. H1N1 flu vaccination is free of post-vaccination adverse events.

e. None of the above is true.

66. HLA screening of patients before starting them on carbamazepine will prevent subsequent hypersensitivity reactions.

a. True

b. False

67. Acute vertigo is always caused by a middle or inner ear disorder.

a. True

b. False

68. Dementia is rarely caused by stroke.

a. True

b. False

69. Hyperglycemia is a poor prognostic sign after acute ischemic stroke.

a. True

b. False

70. Rapid lowering of BP after acute ICH reduces hematoma growth

a. True

b. False

Answers: 62. a, 63. e, 64. e, 65. c, 66. b, 67. b, 68. b, 69. a, 70. a

In Future Issues: **New Treatments for Gliomas**

Clinical Briefs in
Primary Care™
The essential monthly primary care update
By Louis Kuritzky, MD
Supplement to *Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Hospital Medicine Alert, Infectious Disease Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports.*

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Long-Term CV Effects of Intensive Glucose Lowering: The ACCORD Study

Source: Gerstein HC, et al. Long-term effects of intensive glucose lowering on cardiovascular outcomes. *N Engl J Med* 2011;364:818-828.

THE ACTION TO CONTROL CARDIOVASCULAR risk in diabetes (ACCORD) study is really three studies in one, providing information about blood pressure, glucose, and triglyceride treatment in high-risk diabetic patients. Probably the most unsettling component of ACCORD was the early termination of the comparison of tight glucose control (attainment of an A1c < 6) with standard control (A1c 7-7.9) due to an unanticipated INCREASE in mortality associated with tight control. The glucose control arm of ACCORD was designed to go on for 5 years, but intensive glucose control was stopped at 3.5 years. Though various explanations for these results have been offered, none is wholly satisfying.

Once the increased mortality of tight control was appreciated, ALL study subjects were switched to the standard control regimen and followed to the 5-year mark. This most recent publication details outcomes of persons who originally were treated with tight control, and then were switched to standard control for the next 17 months.

Just as had been seen in the initial results of ACCORD, the group that had been assigned to tight control (even though now they had been receiving more relaxed control, and their A1c had risen 7.2%) continued to experience a statistically significant 19% greater risk for death. During Phase 2 of ACCORD, the frequency of hypoglycemia was the same between the standard control group and the group that had changed from tight to standard control; hence, although the greater frequency of hypoglycemia seen in tight control had received some focus as a culprit in inducing greater mortality, this follow-up suggests that is not the case. Why tight control is associated with increased mortality remains unknown. ■

Cysteine as a Biomarker for Sleep Apnea

Source: Cintra F, et al. Cysteine: A potential biomarker for obstructive sleep apnea. *Chest* 2011;139:246-252.

OBSTRUCTIVE SLEEP APNEA (OSA) IS CONsistently associated with cardiovascular misadventure: An increased risk for hypertension, tachycardia, cardiac arrhythmia, myocardial infarction, and stroke has been noted. OSA seems to reset the sympathetic nervous system to a higher level of activity, thus explaining some of these adversities. Tools to identify OSA are somewhat cumbersome and expensive. Were biomarkers available to identify OSA, clinicians could better reserve expensive confirmatory testing for persons with higher pre-test likelihood of disease.

Animal studies have found that sleep deprivation and hypoxia produce elevations in cysteine (CYS). Cintra et al measured CYS levels in subjects undergoing sleep studies (n = 75) and a group of matched controls (n = 75). A non-obese OSA subgroup was included to ascertain whether obesity has an impact on CYS.

CYS levels were significantly higher (15%-17%) in OSA subjects than controls ($P < 0.01$), whether obese or lean. A 6-month period of CPAP treatment resulted in a reduction of CYS levels. No pathogenetic role of CYS is known, but if further studies confirm the relationship between CYS and OSA, it may serve as a reasonable screening tool for selecting those who might benefit from sleep studies. ■

Steroid or Steroid Plus Long-Acting Beta Agonist for Mild Persistent Asthma

Source: Postma DS, et al. Comparison of the effect of low-dose ciclesonide and fixed-dose fluticasone propionate and salmeterol combination on long-term asthma control. *Chest* 2011;139:311-318.

THE LARGEST BODY OF ASTHMATICS IS classified as mild persistent asthma, defined as daytime symptoms more than once weekly but not daily, nocturnal symptoms less than once weekly, and essentially normal lung function between exacerbations. At this stage, long-term controller medications — inhaled corticosteroids (ICS) or leukotriene inhibitors (LKT) — are suggested, reserving combination inhaled corticosteroid/long-acting beta agonist (ICS/LABA) for refractory cases or patients who progress to moderate persistent asthma and beyond. LABA monotherapy is no longer considered appropriate for asthma patients at any stage of disease.

Ciclesonide (CIC) is a novel ICS with

at least two favorable attributes: once daily dosing, and minimal hypothalamic pituitary axis perturbation at typical clinical doses. This clinical trial compared low-dose CIC with low-dose fluticasone/salmeterol in patients with mild persistent asthma (n = 657). The two co-primary endpoints were time to first severe asthma exacerbation and number of poorly controlled asthma days.

CIC alone was not superior to placebo in time to first severe asthma exacerbation, but ICS/LABA was. Other aspects of asthma control were comparable between the two regimens. Although ICS alone is advocated as appropriate initial treatment for mild persistent asthma, this comparison trial suggests that ICS/LABA provides at least one aspect of superiority. ■

Bisphosphonates and Femoral Fractures

Source: Park-Wyllie LY, et al. Bisphosphonate use and the risk of subtrochanteric or femoral shaft fractures in older women. *JAMA* 2011;305:783-789.

ALTHOUGH BISPHOSPHONATES (BIS) HAVE A proven track record for reduction of osteoporotic fracture, reports of so-called "atypical" femoral fracture associated with BIS use has called for re-examination of the risk-benefit ratio of BIS. To do so, a case-control study of more than 200,000 Canadian women who had received BIS was performed. In this population, 716 atypical fractures occurred, and 9,723 typical osteoporotic fractures occurred.

BIS treatment of osteoporosis has been shown to reduce typical fractures by about one-fourth. Since typical fractures are 15-20 times more common than atypical fractures, approximately four times as many more atypical fractures than have been reported would have had to occur to make the risk-benefit ratio unfavorable. Additionally, not all atypical fractures are attributable to BIS use. Finally, the increased risk for atypical fracture was much more common in subjects who used BIS for more than 5 years.

Atypical fractures are an appropriate concern. Nonetheless, the typical fracture risk reduction far outweighs risk of atypical fracture induction. Risk for atypical fracture might be reduced by suggesting a drug holiday after 5 years of BIS use, particularly in women at the lower end of the spectrum of risk. ■

Can Antihypertensive Treatment Benefit Persons Without Hypertension?

Source: Thompson AM, et al. Antihypertensive treatment and secondary prevention of cardiovascular disease events among persons without hypertension: A meta-analysis. *JAMA* 2011;305:913-922.

CLINICAL TRIAL DATA HAVE SHOWN THAT more than one-third of persons with prehypertension (130-139/86-89 mm Hg) will develop frank hypertension over a 4-year interval. Indeed, the lifetime risk of developing hypertension in the U.S. general population is approximately 90%. Although treatment of hypertension provides important risk reduction, clinicians rightfully wonder whether providing antihypertensive treatment to high-risk individuals (e.g., diabetics, persons with manifest cardiovascular disease) — at the stage of prehypertension or even before — might be beneficial.

Thompson et al performed a meta-analysis on 25 clinical trials that treated persons with prehypertension or normotension (total n = 40,395). Antihypertensive treatment classes included beta-blockers, ACE inhibitors, ARBs, calcium channel blockers, and diuretics, either alone or in combination.

Outcomes consistently favored antihypertensive treatment: The relative risk of stroke was reduced by 23%, MI by 20%, CHF by 29%, and all-cause mortality by 13%, all of which were statistically significant. These results suggest that patients at high risk of cardiovascular disease may benefit from use of antihypertensive pharmacotherapies at lower blood pressure than traditionally used as a threshold. ■

More Salt, Fewer Deaths in Diabetes: Who Would Have Thunk It?

Source: Ekinci EI, et al. Dietary salt intake and mortality in patients with type 2 diabetes. *Diabetes Care* 2011;34:703-709.

IN THE GENERAL POPULATION, THERE IS A linear and reversible relationship between salt intake and blood pressure (BP): more salt in begets higher BP, and salt restriction lowers BP. Although it is generally accepted that BP lowering through antihypertensive medications in hypertensive diabetics improves cardiovascular outcomes, whether BP reduction attainable through lifestyle measures, such as salt restriction, might produce similar improvements has not been well documented. Indeed, salt restriction has the capacity to activate neurohumoral systems that are potentially particularly detrimental to diabetics; for instance, salt restriction can activate the sympathetic nervous system and the renin-angiotensin-aldosterone system, and can reduce insulin sensitivity — each of which can be problematic — particularly for diabetics.

Ekinci et al performed a prospective cohort study on diabetics attending a single diabetes clinic (n = 638). Salt intake was ascertained by 24-hour sodium excretion at baseline and each follow-up visit for the ensuing 10-year period of observation.

After adjustment for other risk factors, the relationship between salt intake and mortality was INVERSE. Specifically, for every 100 mmol INCREASE in sodium excretion, all-cause mortality DECREASED by 28%! Arguments about salt have raged for decades; the authors point out that other previous studies (but none previously specifically in diabetics) have NOT consistently found an association between salt intake and mortality. ■

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PHARMACOLOGY WATCH

Supplement to *Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Hospital Medicine Alert, Infectious Disease Alert, Internal Medicine Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports, Travel Medicine Advisor.*

Tiotropium for COPD — The New Standard?

In this issue: Anticholinergic drugs for COPD; pioglitazone for diabetes prevention; insulin degludec in Phase 3 trials; and FDA Actions.

Anticholinergic drugs for COPD

Should anticholinergic drugs be first-line agents for preventing exacerbations in patients with chronic obstructive pulmonary disease (COPD)? The answer may be yes, according to a new study in the *New England Journal of Medicine*. Researchers from Europe compared the anticholinergic drug tiotropium to the beta-agonist salmeterol in more than 7000 patients with moderate-to-very-severe COPD. The study was a randomized, double-blind, double-dummy, parallel-group trial in which tiotropium once a day was compared to salmeterol twice a day. The endpoint was the incidence of moderate or severe exacerbations. Over the 1-year study, tiotropium increased the time to first exacerbation compared to salmeterol (187 days vs 145 days, 17% risk reduction, hazard ratio [HR] 0.83; 95% confidence interval [CI], 0.77 to 0.90; $P < 0.001$). Tiotropium also increased the time to first severe exacerbation ($P < 0.001$), reduced the annual number of moderate or severe exacerbations (0.64 vs 0.72; $P = 0.002$), and reduced the annual number of severe exacerbations (0.09 vs 0.13; $P < 0.001$). Adverse events were similar in both groups. There were 64 deaths in the tiotropium group (1.7%) and 78 in the salmeterol group (2.1%). The authors conclude that in patients with moderate-to-very-severe COPD, tiotropium is more effective than salmeterol in preventing exacerbations (*N Engl J Med* 2011;364:1093-1103). This is the first head-to-head study to show benefit for anticholinergics but it must be pointed out that cardiac patients were excluded from the study, and the annual exacerbation rates were lower than has been seen in other trials. The concomitant use of inhaled corticosteroids was evaluated and did not make a difference in the outcomes. The study was sponsored by Boehringer Ingelheim, the manufacturer of tiotropium (Spiriva). ■

Pioglitazone for diabetes prevention

Pioglitazone reduces the risk of development of diabetes among prediabetic patients, according to a new study. Pioglitazone was compared to placebo in a total of 600 patients with impaired glucose tolerance. After a median follow-up of 2.4 years, the annualized incident rates for type 2 diabetes were 2.1% in the pioglitazone group and 7.6% in the placebo group (HR 0.28, 95% CI, 0.16 to 0.49; $P < 0.001$). Conversion to normal glucose tolerance occurred in nearly half of the pioglitazone group and in 20% of the placebo group ($P < 0.001$) and treatment with pioglitazone was associated with significantly lower fasting glucose levels, 2-hour glucose levels, and hemoglobin A1c levels. Pioglitazone also was associated with a decrease in diastolic blood pressure (2.0 mmHg vs 0.0 placebo), reduced rates of carotid intimal-medial thickening ($P = 0.047$), and an increased level of HDL cholesterol (increase of 7.35 mg/dL vs 4.5 mg/dL; $P =$

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0.008). Pioglitazone caused greater weight gain than placebo (3.9 kg vs 0.77 kg; $P < 0.001$), as well as edema (12.9% vs 6.4%; $P = 0.007$). The authors conclude that pioglitazone reduced the risk of conversion of impaired glucose tolerance to type 2 diabetes but was associated with significant weight gain and edema (*N Engl J Med* 2011;364:1104-1115). Thiazolidinediones have been falling out of favor in recent years for the treatment of type 2 diabetes due to association with edema and heart failure. This new industry-sponsored study suggests that pioglitazone (Actos) is more effective than metformin or lifestyle changes in preventing conversion of prediabetes to diabetes. What is unclear is the effect of these various interventions on long-term diabetic complications. ■

Insulin degludec in Phase 3 trials

Insulin degludec is an ultralong-acting insulin that is currently in Phase 3 trials. It forms soluble multihexamer assemblies after subcutaneous injection, resulting in a very long half-life of up to 40 hours. A new study suggests that it can be used three times a week, achieving blood sugar control equivalent to daily insulin glargine. In a 16-week randomized, open-label, parallel group trial, 245 type 2 diabetics aged 18-75 were randomized to insulin degludec once a day or three times a week, or insulin glargine once a day, all in combination with metformin. At the end of the study, mean hemoglobin A1c levels were similar across the treatment groups at 7.3%, 7.4%, and 7.2%, respectively. The rate of hypoglycemia was low in all three groups. The authors conclude that insulin degludec provides comparable glycemic control to insulin glargine without additional adverse events and may reduce dosing frequency due to its ultra-long action profile (*Lancet* 2011;377:924-931). The study was sponsored by its manufacturer, Novo Nordisk. ■

FDA actions

The FDA has approved the first new drug for lupus (systemic lupus erythematosus) since 1955. Belimumab is a fully human monoclonal antibody the targets human soluble B-lymphocyte receptor stimulator protein. It is indicated for the treatment of adult patients with active, autoantibody-positive lupus who are receiving standard therapy. In two pivotal studies, the drug was found to reduce disease activity compared to placebo plus standard therapy. More deaths and serious infections were reported for belimumab compared to placebo, and it does not appear to be effective in people of African or African American heritage (in whom the disease is three times more common), although more studies are needed to confirm this finding. Belimumab is marketed by GlaxoSmithKline as Benlysta.

The FDA has approved a phosphodiesterase type 4 inhibitor to reduce the number of exacerbations from severe COPD associated with chronic bronchitis. Roflumilast is a once daily oral pill that reduces excess mucus and cough. It does not appear to benefit COPD that involves primarily emphysema. The approval was based on two Phase 3 studies of more than 1500 patients. An accompanying medication guide informs patients of the potential risk of mental health problems including changes in mood, thinking, or behavior, as well as unexplained weight loss. Roflumilast is marketed by Forest Pharmaceuticals as Daliresp.

The FDA has approved a new angiotensin II receptor antagonist, the eighth introduced to the American market. Azilsartan medoxomil is approved for the treatment of hypertension in 40 mg and 80 mg once daily doses. The drug is touted as being more effective in lowering blood pressure than valsartan or olmesartan based on clinical trials. Like other angiotensin II receptor blockers, the drug will carry a box warning regarding pregnancy. Azilsartan is marketed by Takeda Pharmaceuticals as Edarbi.

Zostavax, Merck's vaccine for the prevention of shingles, has been approved for use in individuals ages 50-59. It previously was approved only for those 60 and older. The approval was based on a placebo-controlled trial of more than 20,000 individuals 50-59 years of age. The vaccine reduced the risk of developing shingles in this group by approximately 70%.

The FDA has approved ipilimumab for the treatment of late stage (metastatic) melanoma. The drug is a monoclonal antibody that blocks cytotoxic T-lymphocyte antigen (CTLA-4). The approval was based on a single study of 676 patients with melanoma who had stopped responding to other therapies. When compared to an experimental tumor vaccine, those receiving ipilimumab lived an average of 3.5 months longer (10 months vs 6.5 months). Autoimmune reactions were common including fatigue, diarrhea, rash, endocrine deficiencies, and colitis. Severe to fatal autoimmune reactions were seen in 13% of treated patients. Ipilimumab is manufactured by Bristol-Myers Squibb and marketed as Yervoy. ■

Neurology Alert

2011 Reader Survey

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

Instructions: Mark your answers by filling in the appropriate bubbles. Please write your answers to the open-ended questions in the space provided. Return the questionnaire in the enclosed postage-paid envelope by **July 15, 2011.**

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

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

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

_____

_____

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

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

15. Are the articles in *Neurology Alert*

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

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

_____

_____

Please rate your level of satisfaction with the items listed.

	A. excellent	B. good	C. fair	D. poor
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18. article selections	O A	O B	O C	O D
19. timeliness	O A	O B	O C	O D
20. quality of commentary	O A	O B	O C	O D
21. clearness of abstracts	O A	O B	O C	O D
22. overall value	O A	O B	O C	O D
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26. Which web site related to your position do you use most often?

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

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

O A. yes
O B. no

If yes, how? _____

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