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A Weak Jaw Says Much

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: *Careful testing of jaw muscle power can help to make an accurate clinical diagnosis in acute, flaccid quadriparesis.*

Source: Pal S, Sanyal D. Jaw muscle weakness: A differential indicator of neuromuscular weakness — preliminary observations. *Muscle Nerve* 2011;43:807-811.

GUILLAIN–BARRÉ SYNDROME (GBS), INFLAMMATORY MYOPATHY INCLUDING polymyositis and dermatomyositis (PM/DM), myasthenia gravis (MG), and hypokalemic periodic paralysis (HPP) are among the more common causes of flaccid quadriparesis confronting neurologists in the emergency department. Although often differentiated by characteristic clinical or electrodiagnostic features, this is not always the case, and acute flaccid quadriparesis may present a clinical conundrum to the physician on the neurology ward or emergency department. Do any clinical features permit one to reliably discriminate between these diagnostic possibilities at the bedside?

Between January 2008 and December 2009, patients admitted with acute quadriparesis to the Bangur Institute of Neurosciences, West Bengal, India, were recruited into this prospective, double-blinded study. Exclusion criteria included signs of upper motor neuron involvement or altered sensorium of any cause. Clinical evaluation included thorough neurologic examination with particular attention to strength testing of jaw and neck muscles, blood tests (including acetylcholine [ACh] receptor antibody assay), electrodiagnostic studies (including repetitive nerve stimulation), and muscle biopsy when clinically indicated. Definitive diagnosis was based on repetitive nerve stimulation studies and ACh receptor antibody assay for MG, histopathology for PM/DM, serum potassium level for HPP, and nerve conduction studies for GBS. Statistical analysis included the chi-square test, Fisher exact test, or Monte Carlo approximation, with $P < 0.05$ considered statistically significant.

Among 46 patients who fulfilled the inclusion criteria, GBS was the final diagnosis in 24, generalized MG in 9, HPP in 6, PM in 4, and DM in 3. Weakness of jaw closure was the most clinically reliable diagnostic

Weill Cornell Medical College

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A monthly survey of developments in neurological medicine from the faculty of Weill Cornell Medical College and NewYork-Presbyterian Hospital.

sign, with all such patients having MG. Among MG patients, 88% (8 of 9) had jaw closure weakness. In the absence of jaw closure weakness, weakness of jaw opening became the most significant diagnostic predictor, found in 83.3% (5 of 6) of HPP, and 71.4% (5 of 7) of inflammatory myositis, but only 4.1% (1 of 24) of GBS patients. Among patients with normal jaw strength, 85.2% had GBS, which increased to 100% if areflexia of the legs was present. Weakness of jaw opening but not closing, in the absence of pharyngeal weakness, was diagnostic of HPP. If both jaw opening and pharyngeal weakness were present, PM/DM was the final diagnosis. Jaw muscle weakness is rare in GBS, jaw closing weakness favors MG, and jaw opening weakness PM/DM or HPP.

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Local disorders that affect the trigeminal nerve often result in facial numbness, dysesthesiaes, or paresthesiaes, rather than jaw muscle weakness, and include intra-axial lesions, such as stroke, tumor, demyelinating disease, infections and inflammatory conditions (including collagen vascular diseases such as Sjogren's syndrome, systemic lupus erythematosus, and scleroderma) and extra-axial lesions (including aberrant blood vessels, aneurysms, meningiomas, carcinomatous meningitis, and spread of extracranial primary malignancies). Magnetic resonance imaging usually is warranted in all such instances, and electrodiagnostic tests that may be of benefit include the blink reflex, the masseter inhibitory reflex, the jaw jerk reflex, nerve conduction study of the mental nerve, and quantitative sensory testing of patients with sensory symptoms. ■

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Please call **Leslie Coplin**, Executive Editor, at leslie.coplin@ahcmedia.com.

Can We Make an Accurate Diagnosis of Patients with Posterior Cortical Atrophy?

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: *The use of biomarkers from the CSF, as well as newer PET imaging ligands, allow for an accurate diagnosis in patients who have a syndrome of posterior cortical atrophy.*

Sources: Seguin J, et al. CSF biomarkers in posterior cortical atrophy. *Neurology* 2011;76:1782-1788. Rosenbloom MH, et al. Distinct clinical and metabolic deficits in PCA and AD are not related to amyloid distribution. *Neurology* 2011;76:1789-1796.

POSTERIOR CORTICAL ATROPHY (PCA) IS A CLINICAL SYNDROME that can be the initial presentation of several different neurodegenerative diseases. Initial clinical features typically are referable to occipitoparietal dysfunction, including components of the Balint syndrome (simultanagnosia, ocular apraxia, optic ataxia) or of the Gerstmann syndrome (dysgraphia, dyscalculia, right-left confusion, finger agnosia) or apraxia. In such cases, MRI or FDG-PET will show atrophy or hypometabolism in posterior brain regions. Eventually, other brain regions become involved, depending on the specific underlying disease. The most common pathology underlying PCA is Alzheimer's disease (AD), but corticobasal ganglionic degeneration (CBGD), dementia with Lewy bodies (DLB), and Creutzfeldt-Jakob disease (CJD) also can cause the PCA syndrome and must be considered. Short of brain biopsy, how can one improve diagnostic accuracy in life? In the May 24 issue of *Neurology*, two back-to-back articles demonstrate the usefulness of CSF and imaging biomarkers specific for AD in achieving an etiologic diagnosis for PCA.

CSF levels of Aβ42 are decreased in AD, while levels of tau and phosphotau are increased. When both Aβ and tau are changed appropriately, the results are highly specific for AD. When only one marker is abnormal, the results may still be consistent with AD, although with less certainty. When neither is abnormal, the underlying condition is unlikely to be AD.

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Seguin and colleagues examined CSF levels of tau,

phosphotau, and Aβ42 in patients with clinical diagnoses of PCA (n = 22), AD (n = 160), DLB (n = 69), and frontotemporal degeneration (FTD, n = 68). Overall, the CSF profile of PCA was not different from AD, but clearly was distinct from the other dementias. Of the 22 PCA cases, eight had isolated visual deficits and 11 had visual deficits with memory loss; of these 19 cases, all had abnormalities of both Aβ and tau (n = 16), or abnormalities in only one biomarker (n = 3), consistent with AD as the underlying pathology. The remaining three PCA cases were characterized by asymmetric dystonia, parkinsonism, or apraxia, and were clinically felt to be due to CBGD. Indeed, two of these three cases had normal levels of CSF Aβ and tau, consistent with a non-AD diagnosis. However, in the remaining case both CSF Aβ and tau were abnormal, highly suggestive that AD was the underlying pathology, despite the clinical presentation suspicious for CBGD. Thus, CSF biomarkers were helpful in differential diagnosis.

Rosenbloom and colleagues examined the distribution of amyloid pathology and glucose hypometabolism using PET with the amyloid binding Pittsburgh B compound (PiB) and fluorodeoxyglucose (FDG) in patients with clinical diagnoses of PCA (n = 12), AD (n = 14), and elderly control subjects (n = 30). As expected, subjects with PCA showed greater deficits in glucose metabolism in occipital regions than subjects with AD or normal controls. However, the pattern of PiB binding in PCA was indistinguishable from that in AD. These results are similar to those in which AD presents as a different focal cortical syndrome, primary progressive aphasia (PPA): Although neurodegeneration in PPA is highly asymmetric and preferentially involves the language network, the distribution of PiB binding in AD-associated cases is symmetric and indistinguishable from that in typical AD.

One weakness of both studies is the lack of neuropathologic confirmation. However, both illustrate the potential usefulness of AD biomarkers in discerning the pathophysiologic process underlying PCA. They are very timely, given the recent publication of revised diagnostic criteria for AD by the National Institute on Aging and the Alzheimer's Association. The major advance in these revised criteria is the inclusion of biomarkers in increasing ante-mortem confidence in AD as the correct diagnosis. Biomarker testing may be particularly useful when the clinical presentation is something other than the usual memory-predominant presentation, such as PCA or PPA. In such cases, alternative diagnoses such as CBGD, DLB, or FTD must be considered as well as AD. Adding biomarkers to the diagnostic arsenal will help in correct classification, allowing formerly questionable cases to be entered into clinical trials, and, with the eventual development of more effective therapies, assisting in targeting correct treatment.

One additional research point is raised by the Rosenbloom study. The dissociation between PiB and FDG-PET results indicates that the distribution of fibrillar amyloid does not adequately explain the distribution of neurodegeneration and clinical symptomatology. Determining the other pathogenetic factors involved in focal AD presentations, such as PCA or PPA, may be useful in understanding AD in general. ■

Long-term Impact of Medulloblastoma Treatment in Childhood

ABSTRACT & COMMENTARY

By Adília Hormigo, MD, PhD

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

Synopsis: *Many survivors of medulloblastoma, who were treated with craniospinal radiation, develop physical and cognitive impairments as adults.*

Source: Edelstein K, et al. Early aging in adult survivors of childhood medulloblastoma: Long-term neurocognitive, functional, and physical outcomes. *Neuro-Oncology* 2011;13:536-545.

Medulloblastoma is the most frequent childhood brain tumor and the treatment usually consists of surgical resection and adjuvant craniospinal radiation with chemotherapy. The 5-year survival rate is approximate 80% for the average risk patient. In this paper, the authors analyzed a cohort of 20 adult survivors of childhood medulloblastoma, who were followed for 4 years and underwent physical and neuropsychological evaluation at a median interval of 15.5 years after diagnosis. The patients were treated with craniospinal radiation and 9 patients also received chemotherapy. The investigators noted physical, functional, and neurocognitive deficits. Hypothyroidism was found in 60%, hearing loss in 55%, and secondary neoplasms in 25% of patients. Meningioma was the most frequent of the secondary tumors. Eighty-five percent of the survivors were supported and lived with parents, 90% had frequented programs at school for learning disabilities, and 45% were not competitively employed and attended school full-time. Neurocognitive evaluation showed that working memory, executive function, academic achievement, and motor dexterity were significantly impaired. Furthermore, working memory continued to decline over time. Younger age at diagnosis also was associated with a lower intelligence quotient and less academic achievement.

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*

Early Treatment of Ruptured Aneurysm Improves Outcomes

Source: Phillips TJ, et al. Does treatment of ruptured intracranial aneurysms within 24 hours improve clinical outcome? *Stroke* 2011;42:1936-1945.

INVESTIGATORS AT THE ROYAL MELBOURNE HOSPITAL IN Australia reviewed their 11-year database of consecutive ruptured intracranial aneurysms treated with endovascular coiling or craniotomy and analyzed outcome using the modified Rankin Scale at 6 months. They separated patients into those who were treated within 24 hours (230 cases) and those treated after 24 hours (229 cases). Delay in treatment was due to nonclinical logistical factors. Between the groups, there was no difference in age, sex, smoking history, family history, or size and location of the aneurysm. Poor clinical grade patients were overrepresented in the early treatment group, and increasing age and poor clinical grade were predictors of poor outcome in both groups.

Eight percent of patients treated in < 24 hours were dependent or dead at 6 months compared to 14.4% of those treated > 24 hours, resulting is a relative risk reduction of 44% and an absolute risk reduction of 6.4% (X^2, $P = 0.044$). In addition, 3.5% of cases coiled within 24 hours were dependent or dead at 6 months compared to 12.5% of cases coiled at 1 to 3 days, an 82% reduction in relative risk and 10.2% reduction in absolute risk (X^2, $P = 0.040$). There was no difference in clinical grade in the groups coiled early or late. This study supports the view that treatment of ruptured aneurysms within 24 hours is associated with an improved outcome, and this benefit is more pronounced with coiling. ■

Cerebral Microhemorrhages May Be a Marker for β-Amyloid and Alzheimer's Disease

Source: Yates PA, et al. Cerebral microhemorrhages and brain β-amyloid in aging and Alzheimer's disease. *Neurology* 2011;77: 48-54.

CEREBRAL MICROHEMORRHAGES (MH) FREQUENTLY ARE found in older persons scanned with gradient-echo and susceptibility-weighted MRI (SWI), and have been linked to β-amyloid deposition using Pittsburgh compound B (PiB) PET scanning in patients with Alzheimer's disease (AD) and cerebral amyloid angiopathy (CAA). The authors investigated whether Aβ deposition in healthy elderly individuals is associated with lobar microhemorrhages (LMH).

In a cross-sectional study of 84 elderly healthy controls (HC), 28 subjects with mild cognitive impairment (MCI), and 26 subjects with probable AD, subjects underwent 3-Tesla SWI and PIB PET. Scans were classified as PIB+ or PIB– and MH were counted and classified as lobar or

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This work attempts to assess the consequences of treatment in adult survivors of childhood medulloblastoma. The long-term morbidity of the survivors included chronic physical conditions and cognitive dysfunction. This study has limitations inherent to a retrospective cohort and as such, there is no understanding of when the physical and cognitive impairments started, which started first, how they interrelate, and progress. It is conceivable that auditory impairment could contribute to the development of learning disability and neurocognitive impairments. In addition, it is unclear how much the chemotherapy added to the toxicity of craniospinal radiotherapy and the late effects of treatment. In fact, some researchers are focused on developing therapeutics in which the primary treatment is chemotherapy with bone marrow transplant, with or without craniospinal radiation. Another limitation in this selected cohort is the exclusion of some survivors that might have been followed by a general physician out of the academic medical center where the study took place. Only a prospective study linked to standard treatment or a clinical trial with follow-up to adulthood will be able to answer these questions and assess the severity of deficits. These are important issues for planning future treatments to rescue, prevent, and reduce the disabilities of patients who are survivors of childhood medulloblastoma, and who are expected to live longer, as treatment continues to improve. ■

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3. Sands SA, et al. Neuropsychological functioning of children treated with intensive chemotherapy followed by myeloablative consolidation chemotherapy and autologous hematopoietic cell rescue for newly diagnosed CNS tumors: An analysis of the Head Start II survivors. *Pediatr Blood Cancer* 2010;54:429-436.

nonlobar. Lobar microhemorrhages were found in 30.8% of AD patients, 35.7% of MCI, and 19% of HC. The prevalence of LMH among PIB+ subjects was the same regardless of clinical diagnosis (AD 30.8%, MCI 38.9%, HC 41.4%, $P > 0.7$), and there was a positive correlation between the number of LMH, the intensity of PIB binding, and increasing age. Based on these PIB PET studies, Aβ deposition in older adults is strongly correlated with the presence of lobar microhemorrhages. ■

Intracranial Stenting for High-Grade Symptomatic Stenosis — Not Ready for Prime Time

Source: Fiorella DJ, et al. US Wingspan Registry. 12-month follow-up results. *Stroke* 2011;42:1976-1981. Jiang WJ, et al. Outcome of patients with ≥ 70% symptomatic intracranial stenosis after wingspan stenting. *Stroke* 2011;42:1971-1975.

INTRACRANIAL STENTING FOR SYMPTOMATIC HIGH-GRADE stenosis was heralded with great enthusiasm but has recently been put on hold by the cessation of enrollment in the NIH-supported Stenting vs. Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) #NCT00576692 study because of an unexpectedly high rate of complications in the stent group during the first 30 days (National Institute of Neurological Disorders and Stroke Clinical Alert, April 11, 2011). The SAMMPRIS investigators reported a 14% rate of stroke or death in the first 30 days compared to 5.8 rate in the medical arm. Therefore, the above two papers should be viewed in this context — the randomized study that was designed to answer whether stenting is better than medical therapy already has determined that early complications are more frequent with stenting.

Fiorella et al reported the results of a Wingspan registry of 158 patients from five centers who underwent stenting for symptomatic intracranial lesions of 50%-99% and they reported an average follow-up duration of 14.2 months. The cumulative rate for primary endpoint events (stroke or death) was 15.7% for all patients and 13.9% for those with high-grade stenosis (70%-99%). Of 13 ipsilateral strokes occurring after 30 days, three resulted in death, and 10 of 13 occurred within 6 months of the procedure.

Jiang et al reported a single-center series from Beijing, China, of 100 consecutive patients with intracranial stenosis ≥ 70% and symptoms within 90 days of enrollment. Endpoints were stroke or death within 30 days, or any stroke after 30 days. During a mean follow-up of 1.8 years, nine patients developed stroke (five within 30 days and four afterward). The authors note that their results were favorable when compared to the WASID trial (*N Engl J Med* 2005;352:1305-1316).

The observations from these non-randomized trials, incorporated with the early data from SAMMPRIS, lead us to the conclusion that intracranial stenting for symptomatic stenosis is not ready to be used as standard treatment, and intensive medical therapies are still the preferred approach for symptomatic intracranial stenosis. ■

Natural History of Stroke-Related Homonymous Hemianopsia

ABSTRACT & COMMENTARY

By Marc Dinkin, MD

Assistant Professor of Ophthalmology, Weill Cornell Medical College

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

Synopsis: *Serial examination of Humphrey visual fields in patients with infarct-related hemianopsia shows spontaneous recovery, predominantly in lower quadrants and in the periphery.*

Source: Çelebisoy M, et al. Recovery of visual-field defects after occipital lobe infarction: A perimetric study. *J Neurol Neurosurg Psychiatry* 2011;82:695-702.

NEARLY ONE-THIRD OF STROKE VICTIMS SUFFER FROM HOMonymous hemianopsias related to damage to the optic radiations or occipital cortex. These defects may result in a significant change in quality of life and independence. Following such strokes, patients typically want to know how much improvement there will be and when it will occur. Many are referred to intensive rehabilitation programs aimed at visual restoration, but differentiating therapy-related improvement from spontaneous recovery has been difficult. In this study, neurologists prospectively studied the natural history of homonymous hemianopsia in 32 patients following ischemic stroke, comparing fields acquired within 2 weeks of their stroke to those completed at 6 months. Similar studies had been performed before using either confrontational or manual (Goldmann) visual fields, but this was the first to utilize Humphrey automated perimetry, which allows for a more rigorous statistical

analysis. A mean visual sensitivity score (MVS) was generated for central, mid-peripheral, and peripheral sectors in each quadrant and compared in both the affected and unaffected side. The effect of various locations for the infarct (optic radiation, occipital pole, occipital convexity, cuneus) was analyzed.

Although prior investigations had demonstrated some degree of improvement in > 50% of patients, this study clarified that this applied to defects in the lower quadrants and predominantly in the central and paracentral zones. All zones showed an improvement in the median or maximum MVS for the cohort. Since it is known that visual field improvement occurs by virtue of practice, a comparison was made with the unaffected side where the majority of patients also showed improvement. However, the improvement in the affected hemifields was significantly greater than that of the unaffected fields in the lower zones, suggesting a true improvement in these regions. Interestingly, those infarcts that did not include the striate cortex were associated with a higher chance of recovery, which was most prominent in the paracentral and peripheral zones, most significantly in the lower quadrants. Not surprisingly, patients with smaller lesions containing only one or two of the designated areas showed a greater degree of improvement than those with larger infarcts.

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This study by Çelebisoy et al makes a significant contribution to our knowledge of the spontaneous recovery that occurs after occipital lobe infarcts. The authors confirmed prior findings of (1) greater improvement in the lower quadrants, and (2) more prominent restoration of the fields in the periphery. Their findings stand up to the more rigorous statistical analysis afforded by Humphrey automated perimetry. The gross measurement of percentage change in Messing's paper[1] is replaced with comparisons of quantitative mean deviations in each field region.

It is hypothesized that the greater degree of improvement in the lower quadrants results from supplementary perfusion by the parieto-occipital artery to the superior striate cortex, although no explanation is given for why the presence of redundant perfusion by the posterior temporal artery to the inferior cortex would not have the same effect on superior field recovery. The authors echo Messing's theory that recovery of equal areas of peripheral cortex result in greater visual field recovery than that of central cortex given the greater receptive fields in the periphery.

There were several limitations to this study. First, serial examinations at intermediate time points were not performed, so the timing of the visual field improvement within the 6 months is not elucidated and recovery beyond 6 months cannot be ruled out. Unlike the Messing study, they did not include lateral geniculate lesions or look at hemorrhagic stroke. The schematic divisions of the visual cortex based on Messing's article seem somewhat arbitrary with the medial portion of the occipital lobe designated as striate cortex and the occipital pole delineated as if it is extra-striate. Moreover, no details are offered as to how stroke location was determined based on this scheme or if radiologists were involved. There was no review of the degree of edema, the mechanism of infarction (thrombotic vs. embolic), or the presence or absence of treatment, and their potential relationship with recovery. Finally, since the authors speculated that supplementary blood flow might play a role in recovery, an analysis of the MR angiograms of these patients comparing the degree of redundant circulation with recovery would have helped put that theory to the test.

Despite these limitations, this study remains a strong addition to the relatively small body of literature on the natural history of homonymous visual field defects. Most importantly, it confirms that there is a potential for significant recovery in patients following occipital lobe stroke, giving hope to stroke victims suffering from great disability. It also serves as a reminder that any visual restoration therapy needs to be measured against this spontaneous recovery, so that patients are not made to erroneously attribute such improvement to a timely and often costly rehabilitation program. ■

Reference

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For Cervical Myelopathy from Spondylosis, Which Surgical Approach is Better — Anterior or Posterior?

ABSTRACT & COMMENTARY

By Michael S. Virk, MD, PhD, and Roger Härtl, MD

Dr. Virk is Resident in Neurosurgery, Weill Cornell Medical College. Dr. Härtl is Leonard and Fleur Harlan Clinical Scholar in Neurological Surgery, Associate Professor, Neurological Surgery, Weill Cornell Medical College

Dr. Virk reports reports no financial relationships relevant to this field of study. Dr. Härtl reports that he is a consultant for Synthes and Brainlab.

Synopsis: *In this non-randomized comparative trial, dorsal (posterior) decompressive spinal surgery resulted*

in longer lengths of stay and higher costs compared to ventral (anterior) surgery.

Source: Ghogawala Z, et al. Comparative effectiveness of ventral vs dorsal surgery for cervical spondylotic myelopathy. *Neurosurgery* 2011;68:622-631.

Cervical spondylosis is the most common non-traumatic cause of myelopathy in the cervical spine, and cervical spondylotic myelopathy (CSM) is the most frequent cause of spinal cord dysfunction.[1-3] In 2000, there were 112,400 procedures performed to address degenerative cervical spine disease, a two-fold increase since 1990.[4] The number of patients admitted with CSM doubled between 1993-2002 and 42% of these people underwent spinal fusion, which represents a seven-fold increase over this period.[5] Hospital charges for these procedures exceeded $2 billion in 2000, representing an inflation-adjusted increase of 48%.[4] The incidence of degenerative cervical spine disease increases with age, and as our population ages, so too will surgical treatment and hospital charges. As government and private insurers seek outcomes data and comparative effectiveness studies to use value as the primary measure driving reimbursement, it is of increasing importance to understand which procedures best treat CSM while minimizing complications and cost. Ghogawala et al reported the results of a non-randomized, prospective clinical pilot study comparing ventral and dorsal surgery for treating CSM.[6] Data from such trials is the foundation of evidenced-based practice and guides clinical decision-making. However, study design is challenging and the constraints inherent to these kinds of studies must be understood.

In this pilot investigation, 50 patients were enrolled at seven sites over 2 years (2007-09) with clinical assessments obtained pre-operatively and at 3-month, 6-month, and 1-year intervals post-operatively. A panel of 14 surgeons reviewed each patient's imaging and individually confirmed or rejected eligibility for either ventral (anterior cervical discectomy and fusion) or dorsal (laminectomy with posterior instrumentation and fusion) approach. If a majority of panel surgeons agreed, the case was considered eligible for enrollment. The treating surgeon then met with the patient and together they made the final decision regarding surgical approach. There were two significant differences between the groups. First, patients undergoing dorsal surgery had more severe myelopathy as measured by the Japanese Orthopedic Association (mJOA) score (11.6 vs 13.4; $P = 0.03$). Second, dorsal surgery was performed on more vertebral levels than ventral surgery (3.1 vs 2.6; $P < 0.001$). These differences prohibit direct comparison between the two groups and indicate that the decision to use one surgical approach vs the other was not random. Although both groups showed improvement in the mJOA scores, there was no difference in the amount of improvement when adjusting for baseline. The 30-day complication rate was not significantly different for dorsal or ventral approaches (13.6% vs 17.9%). However, the length of stay was significantly longer for the dorsal approach compared to ventral approach (4.0 vs 2.6; $P < 0.01$), and general health-related quality of life at 1 year improved significantly in the ventral group compared to the dorsal group on 1 of 2 measures (SF 36 Physical Component Summary vs EuroQol-5D). Finally, the mean unadjusted costs were lower for the ventral vs dorsal approach ($19,245 vs $29,465, $P = 0.005$). Given the difference in baseline myelopathy as assessed by the mJOA and the number of levels addressed between the two groups, drawing conclusions from these results is not possible.

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The goals of treating CSM include spinal cord decompression, spine stabilization, restoring alignment or sagittal balance, and minimizing the potential for further degeneration. Despite being grouped into a single diagnosis, each CSM patient presents with unique pathology. For example, disc-osteophyte complexes and ossification of the posterior longitudinal ligament contribute to anterior compression while hypertrophy or buckling of the ligamentum flavum narrows the spinal canal posteriorly. Subluxation and straightening or kyphosis of the cervical spine further contributes to narrowing of the canal. Finally, congenital cervical stenosis diminishes the capacity of any patient to accommodate such degenerative changes and is another independent factor contributing to CSM.

Different surgical approaches vary considerably in their ability to address different etiologies and must be selected appropriately. Primary surgical management of CSM includes anterior cervical discectomy and fusion (ACDF), corpectomy and fusion, laminoplasty, laminectomy alone, and laminectomy with posterior instrumentation and fusion. Additionally, in some cases, a combination of procedures — anterior and posterior — may be required to most effectively treat CSM. For example, corpectomy as well as laminectomy with posterior fusion are most appropriate in cases involving anterior and posterior disease with kyphotic deformity. Restoration of lordosis is important to create sagittal balance by shifting the weight-bearing axis posteriorly and serves to open the spinal canal as well as to slow the dynamic process of degenerative progression. While cord decompression is required to halt ischemic changes thought to underlie myelopathy, biomechanical considerations must be addressed for long-term pain control and prevention of future degenerative change. In addition to CSM etiology, factors such as patient age, medical comorbidities, and number of involved segments all must be incorporated into the decision-making algorithm when selecting the appropriate procedure. ■

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CME Objectives

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

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

CME Instructions

To earn credit for this activity, follow these instructions:

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5. Once the completed evaluation is received, a credit letter will be e-mailed to you instantly. You will no longer have to wait to receive your credit letter!

CME Questions

87. Which of the following statements is *true*?
a. Weakness of jaw closing but not opening, in the absence of pharyngeal weakness, is diagnostic of hypokalemic periodic paralysis.
b. If both jaw opening and pharyngeal weakness is present, Guillain–Barre´ syndrome is the likely diagnosis.
c. Jaw muscle weakness is common in Guillain–Barre´ syndrome.
d. Jaw closing weakness favors a diagnosis of myasthenia gravis.
e. None of the above are correct

88. Biomarkers in the CSF suggest that most cases of posterior cortical atrophy have Alzheimer's disease pathology.
a. True
b. False

89. Which is *false* about adult survivors of childhood medulloblastoma?
a. They have cognitive deficits.
b. They can have functional and physical deficits.
c. Their working memory continues to decline.
d. They rarely have endocrinopathies.

90. Which of the following statements about stroke-related homonymous hemianopia is *true*?
a. Homonymous hemianopia never recovers after a stroke.
b. Lower fields improve more than upper fields.
c. Infarcts in the striate cortex improve more than infarcts in the optic radiations.
d. Active rehabilitation results in better recovery than passive waiting.

91. All of the following statements are true about cervical spondylotic myelopathy (CSM), *except*:
a. Most cases are due to degenerative disease of the spine.
b. CSM prevalence increases with increasing age.
c. Surgical decompression for CSM is of no benefit.
d. Both anterior or posterior decompression may result in improvement.
e. Posterior decompression results in higher hospital costs than anterior surgery.

92. Treatment of ruptured aneurysms within 24 hours results in improved outcomes.
a. True
b. False

93. Cerebral microhemorrhages observed on MRI scans have no clinical significance.
a. True
b. False

94. Intracranial stenting for symptomatic stenosis is better than medical therapy in reducing subsequent stroke risk.
a. True
b. False

In Future Issues: **Autism**

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.*

FDA issues Multiple Drug Warnings

In this issue: FDA issues multiple drug safety alerts; ARBs and cancer risk; and FDA actions.

Avoid high-dose simvastatin

The FDA is advising physicians to avoid high-dose simvastatin (Zocor) because of the risk of myopathy and rhabdomyolysis. The agency is advising that patients should not be started on the 80 mg dose and patients who already are on 80 mg should be continued only if they have been on that dose for 1 year or longer. The recommendations are based on results of the Study of the Effectiveness of Additional Reductions in Cholesterol and Homocystine (SEARCH) trial — a 7-year randomized, controlled trial comparing the efficacy and safety of simvastatin 80 mg vs simvastatin 20 mg with or without vitamin B12 and folate in survivors of myocardial infarction. There was no significant difference in the incidence of major vascular events between the two doses; however, 52 patients (0.9%) in the 80-mg group developed myopathy vs one patient (0.02%) in the 20-mg group. Of the high-dose group, 22 patients (0.4%) developed rhabdomyolysis vs no patients in the 20-mg group. The risk for myopathy and rhabdomyolysis with simvastatin 80 mg was highest in the first 12 months of treatment. Of concern, the risk of myopathy was approximately doubled in patients taking a calcium channel blocker, particularly diltiazem. The majority of patients who developed myopathy also had a genetic variant that affects coding of the transporter responsible for simvastatin uptake in the liver, resulting in higher serum simvastatin levels. The FDA not only recommends against using simvastatin 80 mg, but also suggests that the drug is contraindicated for use in patients taking itraconazole, ketoconazole, posaconazole, erythromycin, clarithromycin, telithromycin, HIV protease inhibitors, nefazodone, gemfibrozil, cyclosporine, and danazol. The maximum dose of simvastatin should be only 10 mg in patients taking amiodarone, verapamil, and diltiazem while the maximum dose is 20 mg in patients taking amlodipine and ranolazine. The new guidance recommends using a different statin if the patient's LDL targets aren't met with the 40-mg simvastatin dose. The loss of high-dose simvastatin comes as a blow to cost-concious consumers who now likely will be prescribed brand name atorvastatin (Lipitor) or rosuvastatin (Crestor). Generic atorvastatin is likely to be available in late 2011. ■

Increased risk of prostate cancer

The FDA has issued a somewhat controversial warning regarding an increased risk for high-grade prostate cancer associated with the 5-alfa reductase inhibitors finasteride (Proscar, Propecia) and dutasteride (Avodart, Jalyn). Ironically, the new warning stems from studies designed to evaluate whether the drugs offer protection *against* prostate cancer. Both drugs are marketed to treat benign prostate hypertrophy and both are known to significantly decrease the prostate-specific antigen levels. In separate studies, both drugs were investigated to see if they reduce the incidence of prostate cancer. FDA experts reviewed the results of the Prostate Cancer Prevention Trial (PCPT), which evalu-

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ated finasteride vs placebo for 7 years, and the Reduction by Dutasteride of Prostate Cancer Events trial (REDUCE), which compared dutasteride to placebo for 4 years. Prostate cancers were significantly reduced in both trials; however, the reduction was limited to low-grade prostate cancers with a Gleason score of 6 or lower. The rate of cancers with a Gleason score of 8-10 was increased in both studies. Previous analyses of these data have suggested that finasteride did not increase the risk of high-grade prostate cancers, but rather made them easier to diagnose by decreasing the volume of the prostate (*Clin Cancer Res* 2009;15:4694-4699; *J Natl Cancer Inst* 2007;99:1366-1374). The FDA panel, however, disagrees and feels it prudent to add a warning to labeling of both medications regarding increased risk of high-grade prostate cancer associated with use of the drugs. The guidance further recommends that prior to initiating therapy patients should be evaluated to rule out other urologic conditions, including prostate cancer, that might mimic benign prostatic hypertrophy. ■

Actos and bladder cancer risk

The diabetes drug pioglitazone (Actos) is the subject of a new warning from the FDA regarding possible bladder cancer risk associated with use of the drug. The FDA ongoing safety review suggests that use of pioglitazone for more than 1 year may be associated with increased risk of bladder cancer based on review of a 5-year interim analysis of an ongoing 10-year epidemiologic study. Patients who had been on pioglitazone the longest and who had the highest cumulative dose of the drug had a slightly increased risk of bladder cancer. This warning falls on the heels of a French study that also showed increased risk of bladder cancer. Based on these findings, France's drug regulatory agency has suspended use of the drug. While the FDA is not recommending withdrawing the drug from the market, it does recommend avoiding pioglitazone in patients with active bladder cancer and using it with caution in patients with prior history of bladder cancer. Thiazolidinediones — including pioglitazone — have also come under scrutiny in recent years because of increased risk of congestive heart failure and bone fractures in females. ■

Chantix and cardiovascular events

The FDA has issued an alert regarding varenicline (Chantix) regarding a small increased risk of certain cardiovascular adverse events in patients who have cardiovascular disease. The warning regarding the smoking cessation drug was the result of review of a randomized, double-blind, placebo-controlled trial of 700 smokers with cardiovascular disease who were treated with varenicline or placebo. The overall rate of adverse effects was low but cardiovascular events, including heart attack, were reported more frequently in the treatment group. The warning will result in a change in labeling for the drug and the FDA is also requiring Pfizer, the drug manufacturer, to conduct an analysis of other trials to further assess the risk. Varenicline already carries a box warning regarding neuropsychiatric symptoms including suicidality. ■

ARBs and cancer risk

Finally some good news from the FDA. After a 2010 meta-analysis showed a possible link between angiotensin receptor blockers (ARBs) and cancer, the agency has completed its own review and has found no evidence of increased risk of "cancer events" including new cancers, cancer-related deaths, breast cancer, lung cancer, or prostate cancer associated with the drugs. The agency conducted a much larger meta-analysis than the original study, including more than 150,000 patients in 31 long-term, randomized, controlled clinical trials. The rate of cancer events in the ARB group was 1.82 per 100 patient years while the rate in the non-ARB group was 1.84 per 100 patient years (relative risk of incident cancer in patients taking ARBs 0.99, 95% confidence interval, 0.92 to 1.06) There was no statistically significant difference in cancer death rates or incidence of individual cancer types. The agency continues to monitor this issue but currently states that the benefits of ARBs continue to outweigh the potential risks (summary available at FDA.gov/drugs/drugsafety/). ■

FDA actions

The FDA has approved the first generic version of levofloxacin (Levaquin). The popular fluoroquinolone is commonly used for treatment of respiratory infections, sinusitis, prostatitis, pyelonephritis and skin infections. Generic forms will include tablets, oral solutions, and injectable solutions.

The FDA has approved an abuse-resistant short-acting oxycodone tablet. Pfizer Pharmaceuticals has licensed the "AVERSION Technology" from Acura Pharmaceuticals. The technology prevents dissolving and injecting tablets by creating a gel when mixed with water or other solvents that prevents snorting crushed tablets by burning nasal passages, and also prevents intentional swallowing of excess quantities by adding niacin which causes intense flushing, itching, and sweating. Long-acting oxycodone (OxyContin) was similarly reformulated in 2010 to prevent misuse and abuse. ■

Clinical Briefs in Primary Care™

The essential monthly primary care update

By Louis Kuritzky, MD

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Fracture Risk Stratification in Diabetics

Source: Schwartz AV, et al. *JAMA* 2011; 305:2184-2192.

It has recently been recognized that type 2 diabetes (DM2) increases risk for osteoporotic fracture, even though it has been demonstrated that DM2 is associated with a paradoxical increase in bone mineral density (BMD) compared to age-matched control populations. With a burgeoning prevalence of DM2 in the United States, almost 20% of the at-risk population for osteoporotic fracture has DM2, hence, clarification of risk stratification for this group is highly relevant.

The World Health Organization (WHO) and the U.S. National Osteoporosis Foundation (NOF) suggest that clinicians assess patient risk for osteoporotic fracture by means of the fracture risk algorithm (FRAX) score. FRAX, an online risk assessment tool (available free of charge at http://www.shef.ac.uk/FRAX/), allows input of patient characteristics including gender, ethnicity, body mass index, risk factors for osteoporosis, history of fracture, family history of fracture, and BMD to calculate a 10-year risk of any osteoporotic fracture as well as 10-year risk of hip fracture. Similar to the structure of the ATPIII lipid guidance, intervention is threshold-based: Anyone with a 10-year risk of hip fracture > 3%, or total fracture risk > 20%, should be considered for pharmacotherapeutics intervention.

Gathering data from three prospective observational studies (n = 9449 women, 7346 men), Schwartz et al studied the relationship between FRAX scores, BMD, and subsequent osteoporotic fractures. Of concern, for any given T-score or FRAX score, the rate of osteoporotic fractures was higher in DM2 subjects than controls. DM2 appears to be a risk factor for osteoporotic fracture, above and beyond what is predicted by BMD or FRAX. ■

Amantadine for Dysphagia in the Elderly

Source: Gokula M, et al. *Ann Long-Term Care* 2011;19:37-40.

When amantadine (AMTD) was an appropriate first-line treatment for influenza, clinicians gained familiarity with its use. In the last decade, influenza resistance to the adamantanes (i.e., AMTD, rimantadine) has essentially eliminated their utility. The safety profile of AMTD is excellent however, heightening interest in clinical use for other syndromes.

Dysphagia in the elderly can be problematic, potentially leading to feeding difficulties and aspiration pneumonia. Probably the two most common scenarios in which we encounter dysphagia are Parkinson's disease and post-stroke, each of which is associated with reduced levels of dopamine. Since AMTD is a dopamine agonist, there is putative rationale for its potential use in dysphagia.

Gokula et al report their clinical experiences with AMTD in elderly patients with dysphagia. Based on positive responses in two test cases, they performed an uncontrolled case series (n = 12) among dysphagia subjects in a long-term care facility using an AMTD dose of either 50 mg or 100 mg/d orally. By 4 weeks, 11 of the 12 subjects demonstrated better swallowing, decreased cough, and weight gain. Additionally, fewer episodes of aspiration were seen.

Because AMTD is generally well tolerated, inexpensive, and there is little other resource for addressing dysphagia, clinicians may wish to consider a clinical trial. ■

Is Homocysteine a Culprit in Aging Skin?

Source: Namazi MR, Feily A. *J Am Acad Derm* 2011;64:1175-1178.

The association of homocysteine (HCST) with atherosclerosis is as strong and consistent as cholesterol, which prompted a flurry of clinical trials in the 1990s and early 2000s attempting to improve cardiovascular outcomes by lowering HCST levels (usually with pharmacologic doses of B vitamins). Unfortunately, HCST modulation did not result in cardiovascular risk reduction, to the point that interventions aimed at HCST have been largely abandoned.

HCST might also, however, be a culprit in aging skin. Photoaging is attributed to up-regulation of cutaneous matrix metalloproteinases and down-regulation of collagen synthesis. Homocystinuria, an inborn error of metabolism characterized by marked elevation of HCST, demonstrates thin, transparent skin.

HCST negatively impacts the three primary structural elements of healthy skin: collagen, elastin, and proteoglycans. Not only does elevated HCST in-

crease degradation of these components, it also inhibits their regeneration.

There have not yet been any clinical trials to examine whether HCST reduction favorably impacts skin aging. ■

Hepatitis C Treatment by Primary Care Clinicians

Source: Arora S, et al. *N Engl J Med* 2011;364:2199-2207.

In most communities in the United States, hepatitis C (HEPc) treatment is provided by gastroenterologists. Because HEPc is now the most common cause of end-stage liver disease, and — unless trends reverse — will continue to be so for the foreseeable future, it is important that identification of HEPc infection be continued vigorously in the primary care community, since most at-risk persons see primary care clinicians as their point of initial contact with the health care system.

Treatment of HEPc offers the opportunity for cure of the disease more than 50% of the time, although persons infected with HEPc genotype I have a somewhat lower success rate. Ideally, treatment would be offered to as many infected persons as possible, yet limitations in specialist consultants who traditionally administer the treatment are an obstacle to access for some patients.

The ECHO program (Extension for Community Healthcare Outcomes) is intended to enhance opportunities for provision of health care to underserved populations through, for instance, videoconferencing technology that allows primary care clinicians to receive case-based education with specialist colleagues. Since 2003, ECHO has resulted in 800 HEPc patients being treated by primary care clinicians. The primary outcome of this ECHO-based trial was sustained virologic response, which is defined as undetectable HEPc RNA 6 months beyond the end of treatment. Encouragingly, analysis of outcomes for patients treated on-site at the University of New Mexico HEPc clinic were essentially identical with those of patients treated at distant sites by clinicians guided though case-based video conferencing. Hopefully, enlarging the spectrum of clinicians who can provide state-of-the-art care for HEPc patients will become a goal for other sites that have the capacity for video conferencing. ■

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COPD Exacerbations: The EXACT Tool

Source: Jones PW, et al. *Chest* 2011;139: 1388-1394.

The impact and consequences of chronic obstructive pulmonary disease exacerbations (COPD-e) are underappreciated. This year, COPD has risen in prominence from the fourth most common cause of death to the third. COPD-e are problematic on multiple levels: as many as 10% of patients admitted for COPD-3 die in the hospital, and the mortality within the year of hospitalization is as much as 20%. Additionally, each COPD-e is associated with a further decline in FEV1 that is not restored once the exacerbation is resolved.

Jones et al have performed the first published formal analysis of COPD-e to derive an instrument known as EXACT (Exacerbations of Chronic Pulmonary Disease Tool).

Based on interviews with COPD patients (n = 410), the authors quantified items pertaining to dyspnea, cough, sputum production, chest discomfort, limitations of activity, fatigue, sleep disturbance, and anxiety associated with COPD symptoms.

Ultimately, 14 items were discerned that quantified COPD-e presence and severity. Hopefully, such a tool could be used in daily diaries of COPD patients to help identify exacerbations at the earliest possible stage so that abortive therapy could be instituted without delay. It remains to be determined whether enhanced early detection and intervention for COPD-e will favorably affect symptomatic control, hospitalizations, or mortality. ■

Are Diabetes Prevention Treatments Truly Disease Modifying?

Source: The DREAM Trial Investigators *Diabetes Care* 2011;34:1265-1269.

Prevention of type 2 diabetes (DM2) is possible by means of several different paths including diet, exercise, metformin, thiazolidinediones, orlistat, acarbose, and valsartan. Although reduced conversion from pre-diabetes to DM2 by as much as 60% has been seen in some DM2 prevention trials, critics point out that it is unclear whether any of the natural history of DM2 — that is, progressive decline in beta cell function — is impacted by currently available interventions. Animal studies have found incretin effects, such as beta cell proliferation and improved beta cell mass, but no persistence of such effects has been confirmed in humans, and most data suggest that none of these favorable effects persist once pharmacotherapy is discontinued. The Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication (DREAM) Trial Investigators published an analysis of glycemic control 2-3 months after cessation of ramipril or rosiglitazone, the agents used in the DREAM trial.

Although the Heart Outcomes Prevention Evaluation trial supported a role for DM2 prevention by ramipril, this was not confirmed in the DREAM Trial, nor was there any beneficial "legacy effect." Although rosiglitazone was effective in DM2 prevention, once stopped, progression to DM2 was similar to placebo. Hence, although prevention of DM2 is achievable with thiazolidinediones, they do not appear to make a sustained impact upon underlying disease pathophysiology since drug cessation is followed by a resumption of declining beta-cell function similar to placebo. ■