Amyloid Plaques Are Surprisingly Dynamic

The amyloid hypothesis of Alzheimer disease predicts that amyloid plaques are a precursor of neuronal damage. However, researchers recently proposed that neuronal damage may precede plaque formation. In this study, the authors used a novel imaging technique to provide insights into the chronology of amyloid deposition in the brains of transgenic mice bred to overexpress human amyloid precursor protein.

The authors monitored brain parenchyma of these transgenic mice weekly and then daily. They observed that fully morphologically typical amyloid plaques could appear within a single day, and develop to their final size within 1 week. Evidence of neuritic dystrophy appeared after the plaques appeared.

Comment:
The development of methods for visualizing amyloid plaques in vivo has led to ongoing revision of our understanding of the biology of these structures. The first surprise, from 3 years ago, was that antibodies against amyloid-β could clear away both deposits and the accompanying neuritic dystrophy in mice (Nat Med 2001; 7:369). This was quite unexpected, because experimental solubilization of deposits has required denaturing concentrations of guanidine. The relevance of rapid plaque turnover in mice to what is certainly a slower process in humans remains unclear. But upending the conventional wisdom led many in the field to contemplate amyloid clearance as a serious therapeutic possibility.

The current findings indicate that plaque deposition can occur just as rapidly as can plaque clearance. This study has become an instant classic, nicknamed the “popcorn plaque” paper among the cognoscenti. The findings reinforce the notion that amyloid plaques are dynamic, again suggesting that they do not result from an unstoppable march of amyloid accretion but, rather, from a process wherein plaques may come and (with manipulation) go. Undoubtedly, the kinetics are different in humans, but again, overturning conventional wisdom enables the contemplation of therapeutic opportunities that might heretofore have been discarded out of hand.

— Sam Gandy, MD, PhD


Predicting Recovery from Smell Loss

This was a longitudinal study of predictors of recovery in 542 people who complained of smell loss due to various causes, including trauma, infection, surgery, and medical treatments. Testing was conducted at baseline (mean time since smell loss, 1.08 years) with the 40-odor University of Pennsylvania Smell Identification Test (UPSIT) and an average of 2.9 years later (range, 3 months to 24 years) with the 40-odor UPSIT or a 12-odor version. (One of the study authors is a shareholder in the company that manufactures the smell test used.)

From baseline to follow-up, 11.3% of anosmic and 23.3% of hyposmic patients regained their age-adjusted sense of smell (although significant improvement occurred in 56.7% and 42.7%, respectively). Age, initial severity of smell loss, and time from onset to baseline significantly predicted the degree of recovery; the cause of initial impairment, elapsed time between tests, gender, and initial smoking habit did not. The authors emphasize the value of quantitative assessment of smell loss, as 87% of the study participants had no smell loss on testing.

Comment:
Smell identification was undertaken by two different methods. The authors acknowledge the possibility, but consider it unlikely, that the loss of sensitivity inherent in comparing the two

TABLE OF CONTENTS

| Amyloid Plaques Are Surprisingly Dynamic | New Brain Tumor Therapies, New Recurrence Patterns |
| Predicting Recovery from Smell Loss | SOX1 Antibodies and Paraneoplastic Lambert-Eaton |
| Does the Vitamin D Emperor Have Clothes? | Myasthenic Syndrome |
| Cortical Demyelination in MS and Progressive Multifocal Leukoencephalopathy | Distinguishing Polymyositis from Inclusion Body Myositis |
| Epilepsy and Mental Retardation in Females: Unusual Inheritance | Restless Legs Syndrome Is Associated with Cardiovascular Disease |
| Effects of Vagus Nerve Stimulation on Cardiovascular Regulation | Diaphragm Shrinkage in Mechanically Ventilated Patients |
| Platelet Aggregometry as a Marker of Risk for Vascular Events: Not Yet | Predicting Outcome in Vestibular Neuritis |
| Venous Sinus Stenting for Idiopathic Intracranial Hypertension | Surgery Beneficial for Lumbar Spinal Stenosis |

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different procedures weakens the overall conclusion; if so, the 12-odor test should have been used on both occasions. Although the analysis suggests that original etiology is unimportant, there were just two major initial causes (upper respiratory infection and head trauma). Idiopathic cases would be difficult to include in an etiology-based analysis. The findings are still useful, but arguably they cannot be applied to all cases of smell loss. Intuitively, it would be remarkable if all causes of anosmia had the same outlook when matched for initial severity. Given that improvements in smell can occur in as little as 3 months, the long intervals between the initial smell loss and baseline for most study participants might explain the apparent prognostic similarity for the different etiologies. The patients who improved after baseline might have been those who were tested earlier in their condition’s evolution than those who fared badly. This is the largest study of smell recovery so far and provides guidance in a hitherto poorly defined area. The findings are clearly valuable in counsel- ing patients and plaintiffs in lawsuits. They counter the widely held belief that olfactory loss is largely irreversible and are consistent with the theory that original cause determines outcome. These results are of value in assessing olfactory disturbance due to trauma and infection. I suspect the prognosis estimate will be less accurate for anosmia related to neurosurgical and neurodegenerative conditions.

— Christopher Hawkes, MD, FRCP

Does the Vitamin D Emperor Have Clothes?

The aim of this study was to examine whether low vitamin D levels correlate with disease activity in multiple sclerosis (MS). Subjects were participants from Turku, Finland, in the PRISMS Study of interferon beta-1a; 15 patients had received either of the two drug dosages, and 8 had received placebo. From serum specimens that had been drawn every 3 months and at time of relapse, up to 64 weeks, the authors measured serum 25-hydroxyvitamin D (25[OH]D), parathyroid hormone, and calcium levels and performed several other clinical chemistry assays in the 23 patients with MS and in 23 healthy laboratory workers (controls).

The authors state that half of all participants had 25(OH)D levels at or below 37 nmol/L (considered deficient) at some point during the year. Levels of 25(OH)D were lower and levels of intact parathyroid hormone (iPTH) were higher during relapses than during remissions. The abstract also states, “All 21 relapses during the study occurred at serum iPTH levels >20 ng/L... whereas 38% of patients in remission had iPTH levels ≤20 ng/L... There is an inverse relationship between serum vitamin D level and MS clinical activity.”

COMMENT:
This simple clinician had some difficulty following the authors’ presentation. The supplementary figure published online plotted vitamin D levels and relapses over a 1-year interval for 12 patients. Relapses did not occur any more often during the presumed high-risk months (8 in December through May, when vitamin D levels are lowest) than during the other months (11 relapses). Figure 2 of the article is a scatter plot of 25(OH)D and iPTH levels from patient specimens drawn during relapse (21) or remission (122). All values for the relapses fit well within calculable confidence intervals for the remission values: Mean vitamin D levels and standard deviations (SDs) were 47±14.4 nmol/L during relapses and 60±21.8 nmol/L during remissions, giving 95% confidence intervals of 19.2 to 75.6 in relapse and 17.3 to 102.7 in remission. For iPTH levels, respective means and standard errors were 33.1 (2.6) ng/L and 26.4 (1.1) ng/L, giving SDs of 11.91 and 12.15 respectively, for 95% CIs of 9.8 to 56.5 for relapses and 2.6 to 50.2 for remissions.

Looking at the authors’ data on measurements by season, the groups did not differ in vitamin D levels. The iPTH peaks, in winter, did differ (41 ng/L in controls, 29 ng/L in patients), but both were well within the cited normal range (15–65 ng/L). Calcium in winter was also within the normal range (2.15–2.51 mmol/L): about 2.35 mmol/L in controls and 2.23 mmol/L in patients.

For all of these comparisons, the finding of statistical significance seems to rely on comparing individual test values rather than patients, and even then by relying on differences in means rather than, say, 95% confidence intervals of
Cortical Demyelination in MS and Progressive Multifocal Leukoencephalopathy

Multiple sclerosis (MS) and progressive multifocal leukoencephalopathy (PML) are both demyelinating CNS diseases. Prior studies have generally focused on the patterns of demyelination in white matter that are induced by these diseases. However, there has been increasing recognition that demyelination involving the cerebral cortex likely contributes to the pathogenesis and clinical symptomatology of both PML and MS.

In this study, the authors provide a detailed pathological comparison of cortical demyelination in MS and PML. They examined postmortem brain material from 13 patients with HIV infection and PML, 4 patients with secondary-progressive MS, 2 patients with HIV encephalopathy, and one control with a non-neurological disease. They classified cortical demyelination, on the basis of lesion location, as leukocortical (affecting gray and white matter and crossing the corticomedullary junction), intracortical (predominantly involving layers III through VI), or subpial (extending from the pial surface into the cortex). Cortical demyelination was found in all PML tissue samples. The lesions were intracortical (60%) and leukocortical (40%), never subpial. The intracortical lesions were found predominantly in middle cortical layers (III through VI) and were frequently small. Leukocortical lesions were less numerous than intracortical ones, were larger, and accounted for a greater proportion of cortical demyelination. Active PML lesions were associated with CD68+ macrophages and monocytes that were often activated (major histocompatibility complex class II+). T-cell (CD3+) density was highest in the white matter of leukocortical lesions. Axon injury (as characterized by interrupted patterns of neurofilament-H protein staining, variation in neurite caliber, and presence of neuritic ovoids and end bulbs) was more common in white-matter lesions than in cortical gray-matter lesions.

Subpial lesions were present in none of the PML samples but in half of the MS samples and accounted for the greatest area of demyelinated cortex in MS. Both MS and PML lesions had many activated macrophages and monocytes and a preponderance of CD3+ cells in the white-matter portion of leukocortical lesions.

Comment:
There are several important conclusions to draw from this study, as the editorialists note. First, the frequency of cortical demyelination in PML had previously been underestimated, likely in part because standard MRI does not allow visualization of cortical demyelination. These cortical demyelinated lesions probably contribute to the “cortical” symptomatology (e.g., altered mental status, aphasia, and seizures) often seen in PML. Second, both the macrophage/microglial and T-cell inflammatory responses differ substantially between gray- and white-matter portions of demyelinated lesions in both PML and MS, suggesting that the mechanisms of injury in these regions also differ. Finally, subpial demyelination is common in MS, but rare to nonexistent in PML and HIV encephalopathy.

—Kenneth L. Tyler, MD

Epilepsy and Mental Retardation in Females: Unusual Inheritance

Epilepsy and mental retardation limited to females (EFMR) is a disorder characterized by convulsions in infancy, mental retardation, and intellectual disability. This disorder has a poorly understood mode of inheritance, whereby seemingly unaffected males transmit it to their daughters. These authors describe the clinical, electrophysiologic, and genetic characteristics of four unrelated families with histories suggestive of EFMR. From 58 family members who provided data, the authors analyzed findings from seizure histories, neurologic examinations, medical records, neuroimaging studies, intelligence assessments, and genetic linkage studies. Information from 27 affected females showed that, on average, seizures began at age 14 months and ended at 12 years. All had convulsive seizures, and two...
thirds had febrile seizures. Clinical presentation, development, and intellect varied widely. EEGs showed generalized spike-wave discharges, focal abnormalities, and diffuse slowing; imaging findings were normal. Autism and obsessive-compulsive disorder were prominent. The authors note that the male carriers showed rigid personalities and behaviors on informal assessments. The candidate gene was mapped to Xq22, but no further localization was possible.

**Comment:** EFMR exemplifies a disease that does not follow typical inheritance patterns. One could postulate a component of the candidate gene on the X chromosome that is activated only in the presence of another X chromosome, or, conversely, inactivated by a Y chromosome. Although the article focuses on the affected females, the “unaffected” males, or the rare unaffected female with the disease locus, may provide better insights into disease mechanism and transmission.

— Autumn Klein, MD, PhD


### Effects of Vagus Nerve Stimulation on Cardiovascular Regulation

The VNS Therapy System (VNS; Cyberonics, Inc.) was approved by the FDA in 1997 as adjunctive therapy for adults and adolescents over 12 years of age whose partial-onset seizures were refractory to antiepileptic drugs, thereby becoming the first (and, to date, only) nonpharmacologic epilepsy treatment recognized by the FDA as safe and effective. Because stimulation of the vagus nerve in the neck may have physiologic and potentially clinically relevant effects via both efferent and afferent pathways, investigators have studied the effects of acute vagus nerve stimulation on vagally mediated functions such as respiration, blood pressure (BP), and heart rate (*Epilepsy Res* 1999; 35:1, and *Respir Physiol* 2001; 127:125). In this study, the investigators used spectral analysis to monitor BP, RR interval (RRI; the time interval between two consecutive R waves on the ECG), and respiration during 60 seconds of continuous VNS (on phase) and 5 minutes of no stimulation (off phase) in 21 epilepsy patients at least 9 months after stimulator implantation. (The typical on-off time of VNS in clinical practice is 30 seconds on and 5 minutes off)

There were no discernible overall effects on diastolic or systolic BP or RRI. However, the low-frequency power of BP and low- and high-frequency powers of the RRI were significantly increased during the on phase compared with the off phase, suggesting VNS-mediated increases in both sympathetic and parasympathetic cardiovascular modulation.

**Comment:** These intriguing findings add to the evidence that VNS has measurable effects on vagally mediated function, presumably via efferent conduction from the site of stimulation. The clinical consequences of these effects — whether beneficial, deleterious, or neutral — remain uncertain, particularly because we do not know whether long-term VNS affects autonomic tone between periods of stimulation, and whether or how VNS might influence cardiovascular modulation when VNS is applied just before or during an actual seizure.

— Steven C. Schacter, MD


### Platelet Aggregometry as a Marker of Risk for Vascular Events: Not Yet

Aspirin plays an important role in stroke prevention, but many patients have recurrent events despite taking it. There is growing interest, therefore, in laboratory tests of effectiveness of aspirin that might be used to target patients for higher doses or for changing to alternative agents. In this study, investigators retrospectively assessed 241 patients referred for platelet aggregometry. All participants had histories of at least one clinical vascular event (stroke, TIA, myocardial infarction, or unstable angina) within the past 5 years and had been taking aspirin for at least 30 days (about half for at least 1 year). To ascertain the outcome — a clinical history of recurrent vascular events during the 5-year interval — the investigators used interviews, questionnaires, and chart review.

There was no association between the results of aggregometry and recurrent ischemic events. However, patients with recurrent events were older and more likely to have hypertension than those with a single episode. The authors conclude that traditional risk factors are more important predictors of recurrence than is platelet function testing.

**Comment:** This study provides a counterpoint to the scant and as-yet unconvincing literature that suggests that platelet function tests may be useful for monitoring patients who take aspirin for vascular prevention. Although the present study has important flaws — including its retrospective design, clinic-based population, and small sample size — it does not demonstrate a role for routine testing of platelet function using aggregometry.

There are problems with all of the existing tests of platelet function, including lack of agreement among assay results, limited evidence of validity compared with aggregometry, and an absence of prospective clinical outcome data. Larger prospective studies using well-validated measures of platelet function are necessary to determine whether laboratory assessment of platelet function has a role in stroke prevention. For now, the clinician should use standard approved doses of aspirin (50–325 mg daily) and spare the expense of additional testing in most patients.

— Mitchell S.V. Elkind, MD, MS


### Venous Sinus Stenting for Idiopathic Intracranial Hypertension

Mounting evidence has demonstrated the presence of venous sinus stenosis in patients with idiopathic intracranial hypertension (IIH). These authors report findings from a single-center case series of 10 consecutive patients who underwent venous sinus stenting for IIH that was refractory to medical treatment. All 10 patients had a stenosis...
at the typical location, the junction of the transverse and sigmoid sinuses, visualized by three-dimensional rotational gadolinium-enhanced magnetic resonance angiography and confirmed by direct retrograde cerebral venography. Eight patients had impaired visual acuity. The mean prestenting pressure gradient across the stenoses was 19.1 mm Hg.

At 3 months after venous sinus stenting, all 10 patients showed normalization of CSF pressures and resolution of papilledema. Headache resolved in six patients, improved in two, and was unchanged in two. Relief was maintained for a mean follow-up of 17 months. Vision was normalized in four patients, improved in three, and unchanged in one. There were no perioperative complications. All stents were patent at 6 months. The authors concluded that venous sinus stenting provides an alternative to classic surgical procedures for treatment of IIH.

**Comment:**
The incidence of idiopathic intracranial hypertension is 1 to 3 cases per 100,000. The disorder carries high morbidity in terms of vision loss and headache. For medically refractory IIH, conventional treatments — lumbar peritoneal and ventriculoperitoneal shunting — remain unsatisfactory, given their high failure rate and need for frequent revision (e.g., Neurology 1997; 49:734). Venous sinus stenting has emerged as a “new kid on the block” for medically refractory IIH. This study adds to a growing literature showing the effectiveness and safety of this approach, regardless of whether venous sinus stenosis is a primary or secondary phenomenon in IIH. The strength of the study lies in the homogeneous clinical characteristics of patients included in the study. The durable resolution of papilledema in all and headache in most patients is compelling. These promising results are similar to those in previously published case series. A prospective controlled study is needed to define the role of venous sinus stenting in the management algorithm for medically refractory IIH in wider clinical practice. — **Dileep Yavagal, MD**


### New Brain Tumor Therapies, New Recurrence Patterns

**A**lthough treatment of malignant gliomas with combination temozolomide chemotherapy, irradiation, and surgery has improved survival, prognosis remains poor and recurrence inevitable. Therefore, the search for novel therapeutic targets continues. Bevacizumab, a human monoclonal antibody, targets vascular endothelial growth factor (VEGF), which mediates angiogenesis in gliomas and other cancers. In this study, researchers retrospectively assessed recurrence patterns in 55 patients with recurrent malignant gliomas who received bevacizumab (along with various chemotherapy regimens) and in 19 patients treated with chemotherapy regimens that did not contain bevacizumab.

Among the 44 patients with radiographic data, the radiographic response rate (i.e., complete or partial tumor regression) with bevacizumab was 34.1%. One third of all bevacizumab recipients had reductions in their steroid doses. Judged by blinded imaging review and by quantitative volumetric analysis of recurrence patterns, there was a trend toward a higher ratio of infiltrative tumor to gadolinium-enhancing tumor in bevacizumab responders compared with nonresponders. The authors conclude that bevacizumab may help suppress enhancing tumor recurrence but not infiltrative tumor growth.

**Comment:**
Bevacizumab combined with chemotherapy for recurrent malignant gliomas has produced striking radiographic response rates in previous studies (Clin Cancer Res 2007; 13:1253). However, the dramatic radiographic changes may not reflect true antitumor activity. Research suggests that bevacizumab may significantly reduce tumor capillary permeability and act as a steroid-sparing agent to decrease peritumoral edema. The authors refer to preclinical studies suggesting that glioma cells co-opt existing cerebral vasculature as an alternative to angiogenesis when VEGF-mediated tumor angiogenesis is blocked. Thus, the volume of contrast enhancement may remain stable, but abnormal FLAIR intensity may increase, reflecting an increase in infiltrating tumor.

The valuable observations in this study are limited by the small number of patients, differing steroid doses and chemotherapy regimens, and lack of definitive differentiation between infiltrating tumor, radiation-related gliosis, and treatment-related leukoencephalopathy in the bevacizumab-treated patients. Nevertheless, they confirm the safety and potential of bevacizumab in glioma therapy, and they highlight potential changes in radiographic tumor-recurrence patterns of which neurologists must be aware. — **Amy A. Pruitt, MD**


### SOX1 Antibodies and Paraneoplastic Lambert-Eaton Myasthenic Syndrome

I**n patients with Lambert-Eaton myasthenic syndrome (LEMS), researchers previously found that 43% of those with small cell lung cancer (SCLC) also had antiglial nuclear antibodies. The same researchers have now conducted further research to identify the antigen of these antibodies and to explore its association with paraneoplastic LEMS. First, they used serum from patients with LEMS, SCLC, and antiglial nuclear antibodies to probe a brain cDNA library. They cloned SOX1, a protein that is involved in neural development and is also native to angiogenesis when VEGF-mediated tumor angiogenesis is blocked. Thus, the volume of contrast enhancement may remain stable, but abnormal FLAIR intensity may increase, reflecting an increase in infiltrating tumor.

The authors then looked for the SOX1 antigen in serum from 105 patients with LEMS (55 with SCLC, 50 idiopathic), 50 with SCLC and anti-Hu–related syndromes, and 50 with SCLC only. They identified SOX1 antibodies in 64% of...
the patients with LEMS and cancer but in none of the patients with idiopathic LEMS (P<0.0001). By contrast, they found SOX1 antibodies in only 32% of the cancer patients with anti-Hu–related syndromes and 22% of those with cancer alone. These findings indicate that the detection of SOX1 antibodies in patients with LEMS predicts the presence of SCLC.

**Comment:**
Patients with nonparaneoplastic Lambert-Eaton myasthenic syndrome are clinically similar to but epidemiologically different from patients with small cell lung cancer and LEMS. In the latter group, robust associations have been established with a history of smoking and with the absence of human leukocyte antigen B8. The current findings demonstrate that SOX1 antibodies are a useful biologic marker for SCLC. This finding is important, because in most patients with LEMS, the neurologic symptoms precede the diagnosis of SCLC, which can be difficult to detect. It is unclear why SCLC patients with LEMS are more likely to have SOX1 antibodies than are other SCLC patients (those with or without other paraneoplastic symptoms). As discussed in an accompanying editorial, SOX1 antibodies have also been associated with SCLC in some patients with limbic encephalitis and voltage-gated potassium channel antibodies. The implication is that, in SCLC patients, the immune response to ion channels (voltage-gated calcium channels in LEMS and potassium channels in limbic encephalitis) is linked to the immune response against SOX1 (an intranuclear protein). This intriguing possibility deserves further study.

—Josep Dalmau, MD, PhD

Sabater I et al. SOX1 antibodies are markers of paraneoplastic Lambert-Eaton myasthenic syndrome. *Neurology* 2008 Mar 18; 70:924.


**Distinguishing Polymyositis from Inclusion Body Myositis**

It is not uncommon for inclusion body myositis (IBM) to be misdiagnosed as polymyositis (PM), largely because the diagnoses hinge on histopathologic features, and physicians therefore often ignore distinctive clinical features. To examine how histopathologic and clinical features correlate in patients with myositis, these researchers used their own combined biopsy and clinical criteria to reexamine muscle biopsies and clinical records of 107 patients who had initially been diagnosed with PM or IBM.

Of the 107 patients, 64 had IBM, 27 had PM, and 16 had clinical features of IBM but lacked histologic features necessary for confirmation. Thus, 37% of patients (16 of 43) who would have been diagnosed as PM on biopsy alone actually had IBM. Nonnecrotic muscle fibers invaded by mononuclear cells were present in 17 of the 27 patients with PM, all 64 with IBM, and 13 of the 16 probable-IBM patients. The authors suggest that invasion of nonnecrotic muscle fibers — advocated by some to be necessary for the histopathologic diagnosis of PM — should not be a required feature.

**Comment:**
Histopathologic features of IBM include endomyosial inflammatory cells, fibers with rimmed vacuoles, small amyloid deposits within fibers, and tubulofilamentous inclusions in the cytoplasm and myonuclei. However, these features are not present in every biopsy and, without a good clinical examination, their absence can lead to misdiagnosis as PM. Characteristically, the earliest muscles affected in IBM are the quadriceps and the flexor forearm muscles. This pattern of weakness is not typical of PM. These observations have led to criteria for definite and possible IBM based on both clinical and histopathologic criteria (Ann Neurol 1995; 38:705 and 1996; 40:581).

The prevalence of PM is unknown, largely because of the lack of universally acceptable diagnostic criteria. Some myopathologists like to see invasion of nonnecrotic muscle fibers to feel more secure about a histopathologic diagnosis of PM, as endomyosial and perivascular inflammation alone is nonspecific and can be seen in other myopathies, such as dystrophies (Lancet 2003; 362:971). In a controversial editorial I coauthored, we suggested that PM exists but is rare (Neurology 2003; 61:288). Many cases referred to me as PM are actually misdiagnosed IBM, dystrophy, or another myopathic disorder. Our editorial emphasized that physicians must perform a good clinical examination and consider these PM mimics before treating patients with possibly harmful immunosuppressive medications.

The current findings, from a large series, support both observations from smaller studies and proposed criteria for definite and possible IBM. Using their own criteria, the authors found that PM is not extremely rare, but they found it the least common of the idiopathic inflammatory myopathies. Invasion of nonnecrotic muscle fibers is not necessary for a clinical diagnosis of PM. We need acceptable consensus criteria for PM to achieve better understanding of the pathogenesis and better treatments.

—Anthony A. Amato, MD

**Restless Legs Syndrome Is Associated with Cardiovascular Disease**

Restless legs syndrome (RLS) is a common (5%-10% of the population) sensorimotor condition that is diagnosed by evaluating patient history. People with RLS experience an urge to move the limbs (often with uncomfortable sensations) that begins or worsens with rest, is worse in the evening, and is at least partially relieved by movement. To determine whether RLS is associated with cardiovascular disease (CVD), investigators conducted a cross-sectional, observational study of 3433 middle-aged and elderly participants in the Sleep Heart Health Study — a community-based assessment of the cardiovascular effects of sleep disorders.

The authors compared the prevalence of CVD in subjects who reported symptoms of RLS and in those who did not (controls). RLS was present in 6.8% of women and 3.5% of men. After adjustments for confounding factors, the RLS patients had an odds ratio of 2.07 for presence of CVD. The association of RLS with CVD was stronger in patients with more frequent or more severe symptoms. The authors conclude that RLS is associated with CVD.
Diaphragm Shrinkage in Mechanically Ventilated Patients

Whether mechanical ventilation causes disuse atrophy in humans has been unknown. To explore this issue, these authors compared biopsy specimens from diaphragms of 14 brain-dead organ donors (case patients; on ventilation for 2 to 3 hours) with biopsy specimens from diaphragms of eight patients undergoing surgery for benign conditions or stage 1 lung cancer (controls; on ventilation for 18 to 69 hours). For the mechanical ventilator should be as short as possible, or even avoided in favor of noninvasive ventilation.

— Eelco F.M. Wijdicks, MD


Predicting Outcome in Vestibular Neuritis

Vestibular neuritis (VN) causes acute vertigo and results from acute loss of function of the superior vestibular nerve due to viral infection. The best test for VN, the caloric test, assesses the input for the horizontal semicircular canal (SCC). But there are other structures of the inner ear that can now be tested.

These researchers prospectively evaluated 51 consecutive patients with unilateral VN using a battery of tests of otolith and of SCC function to determine the involvement of the otoliths (utricle and saccule) and to identify predictors of outcome. Patients were seen within 7 days of onset of acute vertigo with involvement of horizontal SCC based on caloric test but no associated hearing loss, no previous neuro-otologic disorders, and no tumor or stroke found on MRI. Patients were given symptomatic nonsteroid medication and encouraged to resume daily activities. All patients had follow-up visits at 1 week and at up to 8 weeks.

There were three significant findings:

First, all patients initially had horizontal SCC paresis; 82% had ocular torsion (based on fundus photos) and 94% had an abnormal subjective visual vertical, suggesting involvement of the superior vestibular nerve to the utricle; and 49% of the patients had abnormal vestibular evoked myogenic potentials (VEMPs), indicating involvement of the inferior vestibular nerve to the saccule. Second, these otolith abnormalities disappeared faster than did the horizontal SCC dysfunction based on final follow-up. At this time, 25% still had ocular torsion or tilt; 15% had abnormal VEMPs; and 45% to 80% still had SCC deficit. Third, at final follow-up, all patients showed marked improvement in symptoms, but half still reported episodic (16 of 40) or continuous dizziness (4 of 40). A positive head-thrust test at follow-up was the single best predictor of persistent dizziness.

— Brian J. Murray, MD, FRCP(C), D, ABSM


JOURNAL WATCH NEUROLOGY
clinical head thrust, a simple bedside indicator of horizontal SCC function. Whether a persistent head thrust is due to a more severe initial deficit within the superior vestibular nerve or to a lack of central compensation is not clear from the study.

— Ronald J. Tusa, MD, PhD

Surgery Beneficial for Lumbar Spinal Stenosis

These authors’ goal was to document the benefit, or lack thereof, of surgery for symptomatic lumbar spinal stenosis in an intention-to-treat, randomized trial. They studied two groups of patients: 289 who were randomized to surgery or conservative care, and 365 who were in an observational cohort. However, by the final 2-year follow-up, only 67% of patients assigned to surgery had been operated on, and 43% of assigned to nonsurgical (conservative) treatment had had surgery. In the observational cohort, 219 patients chose surgery, and 96% of these had surgery within 2 years.

The primary outcomes, assessed by questionnaire, were bodily pain on the Medical Outcomes Study 36-item Short-Form General Health Survey and physical function on a modified Oswestry Disability Index. An as-treated analysis favored surgery over conservative treatment, with significant differences in both pain and physical-function scores peaking at 6 months and persisting to 2 years.

**COMMENT:** Although the authors also provide intention-to-treat results, the crossovers in this trial mean that only the as-treated analysis is useful. Taken in conjunction with two other recent studies (Spine 2007; 32:1, and Spine 2000; 25:556), these findings suggest that surgery is likely a viable option for patients with spinal stenosis and pain that interferes with their daily activities. Although more than 80% of patients in cohort studies had some symptomatic relief after surgery for spinal stenosis, 7 to 10 years later at least one third reported back pain (Spine 2005; 30:936). Less invasive procedures, such as interspinous distraction and minimally invasive surgical techniques, are promising and may be validated in the future.

These results contrast with those of surgery for lumbar disc herniation, for which there is little difference in the 1-year outcome for those treated surgically versus conservatively (JW Neurology Sep 2007, p. 70, and N Engl J Med 2007; 356:2245). Disk herniations differ from lumbar spinal stenosis in that herniations often shrink, whereas the pathology in lumbar spinal stenosis is largely bony and therefore unlikely to change spontaneously.

— Michael Rontbal, MD