Providing Evidence-based Clinical Information for 22 Years

NEUROLOGY ALERT®

A monthly survey of developments in neurologic medicine

Thomson American Health Consultants Home Page—http://www.ahcpub.com

CME for Physicians—http://www.cmeweb.com

THOMSON
AMERICAN HEALTH CONSULTANTS

INSIDE

Diffusion Tensor MRI in the Diagnosis of ALS

ABSTRACTS & COMMENTARY

Sources: Toosy AT, et al. Diffusion tensor imaging detects corticospinal tract involvement at multiple levels in amyotrophic lateral sclerosis. *J Neurol Neurosurg Psychiatry*. 2003;74:1250-1257; Jacob S, et al. Diffusion tensor imaging for long-term follow-up of corticospinal tract degeneration in amyotrophic lateral sclerosis. *Neuroradiology*. 2003;45:598-600; Sach M, et al. Diffusion tensor MRI of early upper motor neuron involvement in amyotrophic lateral sclerosis. *Brain*. 2003. In press; Ulug AM, et al. Diffusion tensor imaging in the diagnosis of primary lateral sclerosis. *J Magn Reson Imaging*. 2004. In press.

THE DIAGNOSIS OF AMYOTROPHIC LATERAL SCLEROSIS (ALS) AT an early stage can be difficult. It is desirable to have an accurate diagnostic test due to the prognosis of the illness, as well as the potential ability to treat patients earlier. As reviewed recently in *Neurology Alert*, none of the current diagnostic entities have shown high sensitivity or specificity in the diagnosis of ALS. A possible exception to this, however, is diffusion tensor imaging. This was initially shown to have some usefulness in the diagnosis of ALS in 1999. As yet, however, there have been few comprehensive studies that have followed patients or examined its overall sensitivity or specificity.

Several recent reports, however, have verified its efficacy. In Toosy and associates' report, diffusion tensor imaging was used to examine 21 patients with ALS compared to 14 controls. Toosy et al found that the fractional anisotropy and mean diffusivity along the pyramidal tracts from the internal capsules down to the pyramids were significantly different in the ALS group compared to the controls. They did not examine whether any of these measures overlapped between the 2 groups, so one could not assess whether there was any specificity or sensitivity to the measurements. In another study by Jacob and colleagues, tensor diffusion imaging was examined in 3 patients. In the patient who had predominant involvement of upper motor neurons, there was remarkable progressive loss of diffusion anisotropy in the pyramidal tract. This was demonstrated over 9 months. This suggested that it might be a useful measure for studying disease progression. Two patients who had mainly lower motor neuron and bulbar disease did not show any temporal change

VOLUME 22 • NUMBER 5 • JANUARY 2004 • PAGES 33-40

in their diffusion tensor imaging over the 9-month interval. However, they were not compared to controls.

The most interesting recent study is that of Sach and associates. They studied diffusion tensor MRI in 15 ALS patients. That included patients without clinical signs of upper motor neuron lesions compared to healthy controls. They found that there was a negative correlation between the fractional anisotropy and central motor conduction time obtained by transcranial magnetic stimulation. Six of the patients had no clinical signs of upper motor neuron involvement at the time of MRI investigation but developed pyramidal tract symptoms later in the course of the disease. Sach et al found a decrease in fractional anisotropy in the corticospinal tract, corpus callosum, and thalamus of all 15 ALS patients. It, therefore, had 100% sensitivity in these patients.

Ulug and colleagues (including myself) have been conducting studies using diffusion tensor imaging in patients with a diagnosis of primary lateral sclerosis. We have a paper in press on 7 of these patients who met diagnostic criteria for primary lateral sclerosis. We subsequently examined an additional 2 patients. We detected abnormalities in all 9 patients. This test has had 100% sensitivity thus far in diagnosing the primary lateral sclerosis. Using quantitative diffusion anisotropy, there was 100% separation of the primary lateral sclerosis patients from the normal controls. The average diffusion constants also showed a significant separation, but there was slight overlap with the control measurements.

COMMENTARY

Diffusion tensor MRI provides an estimate of the orientation of the white matter integrity on the basis of diffusion characteristics of water. It depends on the orientation of the fiber bundles. Diffusivity is greater in directions along the fiber tract than perpendicular to them. This degree of directionality of diffusion can be measured as fractional anisotropy. This can be very valuable in assessing white matter damage. A feature of ALS as well as primary lateral sclerosis is degeneration in the posterior limb of the internal capsule. It is possible to detect this damage with great sensitivity and reliability using diffusion tensor MRI. In our hands, as well as those in the recent reports in the literature, this has been an extremely valuable test in helping to make the diagnosis in early ALS or primary lateral sclerosis. The clinical picture of some of these patients can be confusing and difficult. In primary lateral sclerosis, the differential diagnosis includes hereditary spastic paraplegia, syphilis, syringomyelia, and spinal multiple sclerosis. In addition, it can be mimicked by patients who have a partial Chiari formation or evidence of cervical spondylosis. These patients can mimic primary lateral sclerosis, and it may lead to unnecessary surgical intervention. A diagnostic test to support the diagnosis of primary lateral sclerosis is, therefore, extremely useful. Similarly, in ALS if one could make the diagnosis reliably and have perhaps a marker of disease progression, this would be extraordinarily useful in diagnosis, as well as a potential surrogate disease marker to be followed with therapeutic interventions. As such, the recent studies using diffusion tensor imaging suggest that this may be an extraordinarily valuable diagnostic tool in patients with both ALS and primary lateral sclerosis. — **M. FLINT BEAL**

Neurology Alert, ISSN 0741-4234, is published monthly by Thomson American Health Consultants, 3525 Piedmont Rd., NE, Bldg. 6, Suite 400, Atlanta, GA 30305.

VICE PRESIDENT/
GROUP PUBLISHER: Brenda Mooney.
EDITORIAL GROUP HEAD: Glen Harris.
MANAGING EDITOR: Robin Mason.
ASSISTANT MANAGING EDITOR: Robert Kimball.
SENIOR COPY EDITOR: Christie Messina Petrone.
MARKETING PRODUCT MANAGER: Schandale Kornegay.
GST Registration Number: R128870672.
Periodicals postage paid at Atlanta, GA.
POSTMASTER: Send address changes to *Neurology Alert*, P.O. Box 740059, Atlanta, GA 30374.

Back issues: $42. Missing issues will be fulfilled by Customer Service free of charge when contacted within one month of the missing issue's date.

Subscriber Information

Customer Service: 1-800-688-2421.
Customer Service E-Mail Address:
customerservice@ahcpub.com
Editorial E-Mail Address: christie.messina@ahcpub.com
World-Wide Web: http://www.ahcpub.com

Subscription Prices

United States
1 year *with* free AMA Category 1 credits: $249
Student/Resident rate: $125
Multiple Copies
2-9 additional copies: $224. 10-20 copies: $199.
Canada
Add 7% GST and $30 shipping.
Elsewhere
Add $30 shipping.

Accreditation

Thomson American Health Consultants (AHC) designates this educational activity for a maximum of 25 hours in category 1 credit toward the AMA Physician's Recognition Award. Each physician should claim only those credits that he/she actually spent in the activity.
Each physician should claim only those hours of credit that he/she actually spent in the educational activity.
This CME activity was planned and produced in accordance with the ACCME Essentials.
AHC is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide CME for physicians.

THOMSON
AMERICAN HEALTH CONSULTANTS

Questions & Comments
Please call **Christie Messina Petrone**, Senior Copy Editor, at (404) 262-5416 between 8:30 a.m. and 4:30 p.m. ET, Monday-Friday.

Statement of Financial Disclosure

In order to reveal any potential bias in this publication, and in accordance with Accreditation Council for Continuing Medical Education guidelines, we disclose that Dr. Apatoff is on the speaker's bureau of Biogen and Teva. Dr. Relkin is on the speaker's bureau of Pfizer, Eisai, and Athena Diagnostics and does research for Pfizer and Merck. Dr. Rubin does research for ASTA Medica and Eli Lilly. Dr. Beal is a consultant for Mitokor and Avicena. Dr. Segal is on the speaker's bureau of Boehringer-Ingelheim. Dr. Plum, Dr. Frucht, Dr. Lado, Dr. Reich, and Dr. Trifiletti report no consultant, stockholder, speaker's bureau, research, or other relationships related to this field of study.

Cervical Artery Dissection: Another Economy Class Syndrome

ABSTRACTS & COMMENTARY

Sources: Lewis MJ, et al. Economy class stroke syndromes: Vertebral artery dissection revisited. *J Neurol Neurosurg Psychiatry*. 2003;74:1594-1595; Touzé E, et al. Risk of stroke and recurrent dissection after a cervical artery dissection: A multicenter study. *Neurology*. 2003;61:1347-1351.

ECONOMY CLASS SYNDROME (ECS) REFERS TO VENOUS thromboembolic episodes among airline passengers

who have remained immobile for long periods in cramped seating that impairs their circulation. Economy class passengers with little leg space are more likely to suffer such events than passengers in roomy first-class seats. The syndrome was first described by Bryan Jennett, professor emeritus of neurosurgery at Glasgow University, who suffered a pulmonary embolism after a lengthy flight.[1]

ECS also has been associated with ischemic stroke in young adults with patent foramen ovale, presumably as a result of paradoxical embolism.[2]

Lewis and associates reported a case of ECS caused by vertebral artery (VA) dissection associated with abnormal neck posture during a 7-hour flight. A 56-year-old man in economy class fell asleep with his head uncomfortably twisted to the right. Upon awakening, he experienced transient (15 minutes) and then persistent weakness and loss of pain and temperature sensation of his right arm and leg but not of his face or tongue. Brain MRI confirmed an acute left medial medullary infarct. Contrast-enhanced MR angiography demonstrated dissection of the left VA at the level of the second cervical vertebra and along its length to its junction with the basilar artery. Following treatment with antiplatelet agents and rehabilitation, the patient made a full clinical recovery.

In this case, trivial trauma, perhaps coupled with a disorder of the arterial wall, led to VA dissection and stroke. An important question to be answered is whether the patient is subject to a recurrence of dissection in the previously dissected and healed VA or in another cervical artery not previously involved. The recurrence of dissection in a healed artery is considered uncommon but can occur in another artery previously not dissected. A previous study[3] found the recurrence of dissection at 10 years to be about 12% for all age groups, while the recurrence rate for patients younger than 45 was 17%. Cervical artery dissection occurs less frequently in the elderly, perhaps because atherosclerotic vessels are less susceptible to dissections.

Touzé and associates studied a historical cohort of more than 450 patients (mean age, 44 years) with cervical artery dissection followed for a mean of 31 months. Carotid artery dissections (384) were twice as common as VA dissections (170). Seventy-two patients (16%) had multiple dissections. The initial presentation was an ischemic stroke in 64%, transient ischemic attack in 12%, and subarachnoid hemorrhage in 1%. One quarter of patients had only local signs (ipsilateral headache, neck pain, Horner syndrome, pulsatile tinnitus, etc). The recurrence rate for stroke (0.3% per year) was very low. The incidence of cervical artery dissection recurrences was difficult to assess because some recurrent dissections are asymptomatic. Only the presence of multiple dissections at the initial presentation was significantly associated with an increased risk of ischemic event (hazard ratio, 4.2).

COMMENTARY

The term "economy class syndrome" has acquired general currency because it reflects the experience and anxieties of air travelers. The possibility of lower-extremity deep-vein thrombosis (DVT) during a lengthy airline flight (although the malady also can affect passengers on long train, bus, or car trips) emphasizes the need for passengers to take preventive measures such as moving about the cabin, doing in-seat exercises, etc.

Because of the primary association of ECS with venous thromboembolism, I do not believe that cervical artery dissection should be considered part of the syndrome. Dissections of cervical arteries tend to occur spontaneously in patients with underlying arterial disease and, unlike DVT, are not significantly associated with cramped seating.

The very low risk of stroke and recurrent cervical artery dissection reported by Touzé et al is welcome.

I have resolved to travel business class on all future flights for health-related reasons. — **JOHN J. CARONNA**

References

1. Cruickshank JM, et al. *Lancet*. 1988;2:497-498.
2. Isayev Y, et al. *Neurology*. 2002;58:960-961.
3. Schievink WI, et al. *N Engl J Med*. 1994;330:393-397.

Ximelagatran vs Warfarin: Is There a More Convenient Option for Anticoagulation in Atrial Fibrillation?

ABSTRACT & COMMENTARY

Source: Olsson SB; Executive Steering Committee on behalf of the SPORTIF III Investigators. Stroke prevention with the oral direct thrombin inhibitor ximelagatran compared with warfarin in patients with non-valvular atrial fibrillation (SPORTIF III): Randomized controlled trial. *Lancet*. 2003; 362:1691-1698.

SPORTIF V

Warfarin, a compound initially introduced in 1948 as rat poison, has been the mainstay of anticoagulation for

more than 50 years. Patients with atrial fibrillation (AF) require warfarin for stroke prophylaxis, but many shy away from the perceived stigma of this medication and the demanding blood monitoring program it requires. New alternative anticoagulants now exist that may be equally efficacious as warfarin and allow a more convenient fixed dosing schedule with a superior safety profile.

Taking its cue from the medicinal leech, Hirudo medicinalis, the compound ximelagatran (trade name Exanta™) acts as a direct thrombin inhibitor. It has been studied in a series of multicenter trials known as SPORTIF (Stroke Prevention using an ORal Thrombin Inhibitor in atrial Fibrillation). SPORTIF III was published in *Lancet* in November 2003. In this study, 3410 patients with AF and 1 or more stroke risk factors were studied over a period of 1 year or more, randomized to either ximelagatran or open-label warfarin (at an INR range of 2-3). The primary event rate defined as all stroke (ischemic or hemorrhagic) occurred at a rate of 2.3% per year on warfarin compared to 1.6% per year on ximelagatran. This represented a relative risk reduction of 29% (which did not reach statistical significance). The risk of major and minor hemorrhages was significantly lower with ximelagatran (25.8% per year) than with warfarin (29.8% per year). This was primarily minor bleeding with major bleeding limited to approximately 1.5% in both groups. Abnormalities in liver function tests (elevations in alanine aminotransferase [ALT] greater than 3 times normal) occurred in 6% of ximelagatran-treated patients compared to 1% on warfarin ($P < .0001$).

The results of SPORTIF V were also recently released at the November 2003 meeting of the American Heart Association. This study differed slightly from SPORTIF III in that a double blind was maintained, with either real or "sham" dose adjustments made for patients on warfarin, as well as those on fixed-dose ximelagatran. SPORTIF V included 3922 patients with AF, with an event rate of 1.6% per year on ximelagatran compared to 1.2% per year on warfarin, a nonsignificant difference. The incidence of bleeding (combined major and minor events) was significantly lower with ximelagatran (37% compared to 47% on warfarin [$P < .0001$]). As in SPORTIF III, there was a transient increase in liver enzymes, which resolved over 2-6 months, regardless of whether ximelagatran therapy was maintained or discontinued.

COMMENTARY

When taken together, pooled analysis of SPORTIF III and V in the total group of 7329 patients shows an overall event rate of 1.6% for both drugs. The SPORTIF investigators have successfully demonstrated clinical equivalence between ximelagatran and warfarin. Indeed, ximelagatran may be safer from a bleeding perspective; however, the observed incidence of liver function abnormalities may be unacceptable. While no clinically significant liver disease has been documented, patients who take ximelagatran would require years of therapy, and long-term safety data are lacking. Neither should the issue of cost be ignored, as it is likely that this agent will be many-fold more expensive than generic warfarin. Perhaps this cost will be offset by avoiding years of laboratory fees for INR measurements. Should ximelagatran meet with FDA approval in the coming months, it may fall on the shoulders of clinicians to be the final arbiter of this complex risk-benefit calculus. — **ALAN Z. SEGAL**

Smoking Increases Risk for Multiple Sclerosis

ABSTRACT & COMMENTARY

Source: Riise T, et al. Smoking is a risk factor for multiple sclerosis. *Neurology*. 2003;61:1122-1124.

In this epidemiologic analysis of 22,312 individuals living in Norway, a total of 87 reported having developed multiple sclerosis (prevalence rate, 390 per 100,000). Most patients with MS who were former smokers and all who were current smokers had started smoking before the onset of multiple sclerosis. The risk of developing multiple sclerosis was significantly higher among smokers than among never-smokers (rate ratio, 1.81; 95% CI, 1.1-2.9; $P = .014$). This was higher than the relative risk of smoking for stroke (rate ratio, 1.48; 95% CI, 0.94-2.35).

COMMENTARY

This study validates our clinical anecdotal observations about smoking and multiple sclerosis and identifies an important environmental variable that can be controlled to reduce the risk of multiple sclerosis in a person's lifetime. A previous prospective study of a large cohort of female nurses showed an increased frequency of MS in smokers in a dose-dependent fashion.[1] This dose-response relationship from Riise and associates' study is still in analysis. Nonetheless, it is reasonable to expect that smoking is a significant comorbidity in the onset and disease severity of multiple sclerosis. Patients with multiple sclerosis should be strongly counseled to stop smoking. — **BRIAN R. APATOFF**

Reference

1. Hernan MA, et al. *Am J Epidemiol*. 2001;154:69-74.

Going to Pot with MS?

ABSTRACT & COMMENTARY

Source: Zajicek J, et al. Cannabinoids for treatment of spasticity and other symptoms related to multiple sclerosis (CAMS study): Multicenter randomized placebo-controlled trial. *Lancet*. 2003;362:1517-1526.

In this randomized, placebo-controlled trial of 15 weeks' duration, 667 patients (mean age, 50; mainly EDSS 6-9) with stable advanced multiple sclerosis (MS) were assigned to 1 of 3 groups: oral cannabis, oral tetrahydrocannabinol (THC), or placebo. Tablets were dosed according to body weight, approximately 0.25mg/kg, on average 6-8 of the 2.5 mg THC (Marinol) tablets on a b.i.d. divided-dose schedule. There was no treatment effect on the primary outcome (P = .40) of spasticity scores using the Ashworth scale. The estimated difference in mean reduction in the Ashworth spasticity score for patients taking cannabis extract vs placebo was 0.32 (95% CI, -1.04 to 1.67) and for those taking THC vs placebo was 0.94 (95% CI, 0.44 to 2.31). There was, however, evidence of a treatment effect on patient-reported spasticity and pain (P = .003). The improvement in self-reported spasticity occurred in 61% of patients on cannabis extract, 60% on THC, and 46% on placebo. There was also a suggestion of benefit in the 10-m timed ambulation.

COMMENTARY

Spasticity is a complex symptom with components of increased tone or stiffness, often complicated by pain limitations in mobility. Although no objective improvement in spasticity scores could be documented in this trial, the subjective self-reported benefits of cannabinoids could be meaningful in patients dealing with painful symptomatology of advanced disease. — **BRIAN R. APATOFF**

Prions and Mesial Temporal Lobe Epilepsy: Not the Usual Suspects

ABSTRACTS & COMMENTARY

Sources: Walz R, et al. Surgical outcome in mesial temporal sclerosis correlates with prion protein gene variant. *Neurology*. 2003;61(9):1204-1210; Mastrianni JA, Roos RP. Wrinkles and folds of the prion protein. *Neurology*. 2003;61(9): 1168-1169.

Allelic variants of the cellular prion protein (PrPc), the product of the prion protein gene (PRNP), are best known for their role in spongiform encephalopathies. In an entirely novel observation, Walz and associates describe a PrPc variant associated with hippocampal sclerosis that seems to be partially predictive of seizure-free outcome in patients undergoing surgery for medically refractory mesial temporal lobe epilepsy (MTLE).

Walz et al studied a population of 100 consecutive patients surgically treated for medication-resistant MTLE. These patients underwent resection of the anterior-lateral temporal pole on the epileptogenic side to a maximum of 4-5 cm posteriorly, further allowing access to removal of mesial temporal structures up to 3 cm back. One hundred and eighty control individuals, without a history of neurologic or psychiatric disease, were also included. DNA samples were obtained, and 4 PRNP polymorphic alleles, occurring at different frequencies, were identified among the cases. Among these, a heterozygous genotype (Asn/Ser) involving an asparagine to serine substitution at codon 171 (Asn171Ser) was found among the epilepsy cases. This genotype was present in 23 of the patients, compared to none of the controls (P < .0001). While the Asn/Ser genotype did not correlate with any of the demographic or presurgical data, the Asn171Ser allele was associated with a lower rate (68.2% vs 91.8% for Asn/Asn) of seizure freedom at 18 months postoperative follow-up (P = .005).

COMMENTARY

PrPc is a glycoprotein expressed on the cell surface of neurons, including synapses. Its normal function is unknown, but it is clear that certain allelic variants create protease-resistant forms that lead to the prion diseases: Creutzfeldt-Jakob disease (sporadic, iatrogenic, and variant), kuru, fatal familial insomnia, etc. Two important preclinical observations motivated the current study investigating the possible association of PRNP polymorphisms with MTLE: 1) PRNP knockout mice appear to have enhanced sensitivity to developing seizures;[1] and 2) hippocampal slices prepared from these animals demonstrate neuronal hyperexcitability.[2]

As suggested by the accompanying editorial by Mastrianni and Roos, the human data need to be interpreted with caution, specifically relating to population sampling (eg, inadequate sample sizes or sample populations that have different ethnic origins or skewed genetic backgrounds). While Walz et al indicate that the ethnic backgrounds of patient and control groups were similar, it is still critical to replicate their findings among different ethnic groups.

The current report shows the promise of using a differ-

ent level of genetic study for non-Mendelian presumably multigenic diseases, such as epilepsy. Older methods are certainly complementary, such as linkage analysis, coupled with looking for candidate genes located close to associated polymorphisms. These studies, however, require large pedigrees of affected individuals surrounding an index case. On the other hand, Walz et al's analysis allows us to look at broader populations of affected individuals. While not used in the current study, microarray analysis will also allow screening larger samples of candidate genes. While patient populations studied in this way may be more phenotypically heterogeneous, this may provide a subtle benefit in allowing investigators to begin to tease out the different contributions of nature vs nurture that can account for the fact. For example, the Asn171Ser allele leads to 68.2% surgical cure rather than complete surgical failure. — **ANDY DEAN**

References

1. Walz R, et al. *Epilepsia*. 1999;40:1679-1682.
2. Mallucci GR, et al. *EMBO J*. 2002;21:202-210.

Sjögren Syndrome and Neuropathy

ABSTRACT & COMMENTARY

Source: Gorson KC, Ropper AH. Positive salivary gland biopsy, Sjögren syndrome, and neuropathy: Clinical implications. *Muscle Nerve*. 2003;28:553-560.

WHAT CHARACTERISTICS OF A NEUROPATHY MAKE Sjögren syndrome the likely diagnosis? Sjögren syndrome may be defined as a tetrad of dry mouth, dry eyes, positive serology (antinuclear antibody [ANA], rheumatoid factor [RF], or anti-SSA/SSB), and positive minor salivary gland biopsy. Peripheral neuropathy is commonly associated. Between 1995 and 2001, 54 consecutive neuropathy patients were seen for diagnostic evaluation that included lip biopsy. Criteria for lip biopsy comprised 1) idiopathic polyneuropathy; 2) sicca symptoms in a patient with idiopathic polyneuropathy or a second possible cause for neuropathy (lupus, monoclonal gammopathy of undetermined significance, mixed connective tissue disorder, ethanol abuse, hyperlipidemia, celiac disease); or 3) positive Sjögren serology (ANA > 1:160, RF >1:160, or positive anti-SSA/SSB antibodies). Exclusionary criteria included a previous diagnosis of Sjögren syndrome, lymphoma, AIDS, or sarcoidosis. All patients underwent electrodiagnostic studies. Biopsy interpretation was performed by a pathologist, blinded to the clinical information. Positive diagnosis required at least 2 foci of inflammatory cells defined as a cellular infiltrate of 50 or more lymphocytes. Non-neuropathy patients (n = 38) with sicca symptoms or salivary gland tumor or swelling who underwent lip biopsy served as controls. Statistical analysis was provided by Fisher's exact test, the Kruskal-Wallis analysis of variance, or the Wilcoxon matched sign rank test, with a P value of < 0.05 considered significant.

Twenty patients (37%) were biopsy positive for Sjögren syndrome and had a shorter duration of symptoms (mean, 27 months vs 44 months), with more frequently expressed systemic complaints (rash, joint pain, Raynaud's syndrome) than biopsy-negative patients. No significant difference was seen with respect to the frequency of sicca symptoms, neuropathy severity or distribution, or motor or sensory scores using the MRC and modified Neurological Impairment Scales. Neuropathy in biopsy-positive patients was most often a painful distal predominantly small-fiber sensory axonal neuropathy (n = 7), but painless sensory or sensorimotor polyneuropathy (n = 6), mononeuritis multiplex or painless sensory ataxic neuropathy (n = 3, each), and combined painful neuropathy with sensory ataxia (n = 1) were also seen. Anti-SSA/SSB positivity, ANA > 1;160, or any serological abnormality of ANA, RF, or SSA/SSB were more common in the biopsy-positive group, but elevated ESR or cerebrospinal fluid protein were not. Only 5 biopsy-positive patients had all components of the diagnostic tetrad. Four of 38 controls (11%) were biopsy positive but significantly less so ($P < .007$) than neuropathy patients. Lip biopsy should be considered in idiopathic polyneuropathy even in the absence of sicca symptomatology, and positive biopsy would suggest a diagnosis of neuropathy secondary to Sjögren syndrome.

COMMENTARY

Genetics, hormones, environmental factors, and infectious agents are believed to play a role in the pathogenesis of Sjögren syndrome.[1] Human leukocyte antigens (HLA) confer a specific genetic susceptibility in certain populations and appear to affect autoantibody formation as well. Interleukin-10 promoter polymorphisms remain controversial regarding a role in Sjögren etiopathogenesis. Male fetal cells and DNA have been detected in almost 50% of salivary gland biopsies in one Sjögren study, supporting a role for microchimerism in generating autoimmunity. Strong female gender bias in Sjögren syndrome underscores the importance of sex hormones in immunoregulation, but their precise role

remains unclear. Viruses, including Epstein-Barr, hepatitis C, HTLV, and other retroviruses, may trigger Sjögren syndrome, but this raises an interesting conundrum as diagnostic criteria for the syndrome specifically exclude sicca symptoms associated with distinct viral infection such as AIDS. Understanding the cause of this condition awaits further investigation. — **MICHAEL RUBIN**

Reference

1. Hansen A, et al. *Curr Opin Rheumatol*. 2003;15: 563-570.

Best Office Test for Quadriceps Weakness

ABSTRACT & COMMENTARY

Source: Rainville J, et al. Comparison of four tests of quadriceps strength in L3 or L4 radiculopathies. *Spine*. 2003;28: 2466-2471.

THIRTY-THREE CONSECUTIVE PATIENTS WITH L3 OR L4 radiculopathy were compared to 19 controls of comparable age to determine the best method for detecting quadriceps weakness in the office setting. Controls had either L5 or S1 radiculopathy to allow for the effect that pain might have in preventing full effort. Radiculopathy was in all instances documented by magnetic resonance or computerized tomographic scan, demonstrating compression of the appropriate nerve root. Patients were excluded if they had bilateral radiculopathy, peripheral neuromuscular disease, physical signs suggesting nonorganic amplification of symptoms, hip or knee arthritis, cancer, or psychiatric disorders. Four testing methods were studied: 1) The single leg sit-to-stand test, with the seated patient asked to extend one leg, hold that foot above the floor, and rise to the standing position with the other leg. The examiner could hold the patient's hands for balance; 2) The step-up test, with the patient stepping up onto a standard 7-inch step-stool, again holding the examiner's hands for balance; 3) The knee-flexed manual muscle test, with the patient supine, the hip flexed to 90°, the knee maximally flexed, and the patient attempting to extend the knee against the examiners resistance; and 4) The knee-extended manual muscle test, as in the knee-flexed manual muscle test but with the knee extended and the examiner trying to overcome knee extension. Reliability of findings was enhanced by a second examiner separately performing the identical examination. Statistical analysis was performed using frequency and means calculations, with kappa values calculated to determine inter-rater reliability.

The single leg sit-to-stand test was the most sensitive, with positivity in 61% (20/33). None of the controls failed this test. Knee-flexed and knee-extended manual muscle testing was positive in 42% and 9% of patients, respectively, with 1 control having weakness on the former. Step-up onto stool testing was positive in 27% of patients (9/33) but in no controls. Single-leg sit-to-stand quadriceps testing should be incorporated into the neurologic exam of suspected L3 or L4 radiculopathy where standard muscle tests fail to demonstrate quadriceps weakness. Suspected femoral neuropathy would be another scenario where this would be useful. Knee-extended manual muscle testing of the quadriceps is a waste of time.

COMMENTARY

How might sensory deficits be quantified in radiculopathy? Forty-eight patients with lumbosacral radiculopathy, secondary to magnetic resonance-documented L5 or S1 unilateral disc herniation, were examined using current perception threshold (CPT) evaluation to study A-beta, A-delta, and C fiber function.[1] Using a neurometer device, 3 electric current frequencies, 2000, 250, and 5 Hz, were administered to the L5 and S1 dermatome on the dorsal side of the first and fifth metatarsal, respectively. A visual analog scale was used to score pain intensity. Eleven healthy volunteers served as controls, and both legs were studied in all subjects.

Among radiculopathy patients, CPT values were significantly higher, at all frequencies, in the affected leg compared to the contralateral leg. Compared to controls, values were higher at 2000 and 250 Hz but not at 5 Hz. No significant CPT difference was found between the left and right legs in controls for any frequency. CPT testing may be useful to quantify small-fiber sensory nerve dysfunction in patients with radiculopathy. — **MICHAEL RUBIN**

Reference

1. Yamashita T, et al. *Spine*. 2002;27:1567-1570.

Once Upon a (Medium-Firm) Mattress

ABSTRACT & COMMENTARY

Source: Kovacs FM, et al. Effect of firmness of mattress on chronic non-specific low-back pain: Randomised, double-blind, controlled, multicentre trial. *Lancet*. 2003;362: 1599-1604.

RIGHT UP THERE ALONGSIDE "EATING AN APPLE A day" and "not walking outside with wet hair on a

cold day" is the other widely held "medical truth" that "a firm mattress is good for your back." While the first 2 tenets are largely discounted by anyone with some medical training, the virtues of a firm mattress are generally espoused by the medical and lay community alike—that is, despite the utter lack of scientific evidence to support it. In an attempt to shed light on this poorly understood subject, Kovacs and associates assess the effect of the firmness of a mattress on low back pain.

In a double-blind, multicenter trial, 313 adults with chronic nonspecific low back pain were randomized (with 310 patients available in the intention-to-treat analysis) to use a firm mattress vs a medium-firm mattress. Inclusion criteria included adults older than 18 with nonreferred low back pain not related to an underlying disorder such as trauma, cancer, or infection. Patients taking analgesics dosed in the evening or lasting 24 hours were excluded. Mattress firmness was based upon the European Committee for Standardization rating scale. Patients were randomly assigned to a firm mattress (scored 2-3) or a medium mattress (scored 5-6). Outcomes were measured at 90 days with the primary end points including pain while lying in bed; pain upon arising; and disability. Self-assessment of pain was made using the visual analogue scale (VAS), and disability was assessed with the Roland Morris 24-item disability questionnaire.

The results at 90 days showed that both groups experienced improvements compared to baseline. As for comparisons between groups, on the "pain while lying in bed" measurement, the firm group improved 70% compared to an 80% improvement in the medium-firm group (P = ns); both improved 57% with respect to "pain upon rising"; and patients in the medium-firm group had a superior improvement in disability of 30% vs 50% (P = .008). Kovacs et al note that 77% of patients in the firm group accurately perceived the firmness of their mattress, whereas 43% of the medium-firm group also believed they were on firm mattresses. If this confounding variable is removed, the improvement of the medium-firm mattress over the firm nearly doubles.

COMMENTARY

Consider that in order to do this study, Kovacs et al had to actually purchase new firm or medium-firm mattresses for each subject. At an average price of $500, this low-tech experiment ending up costing a minimum of $150,000, not counting a group purchase discount. But the point remains that such a seemingly simple study is in practice very hard to do. As with many provocative studies, more questions are raised than answered. What were the actual firmness measures of the baseline mattresses and did the degree of increase in firmness correlate best with improvement? Indeed many more issues can be raised, but for now let us consider the possibility that an apple a day doesn't necessarily keep the doctor away, that you don't catch a cold from being cold, and that a medium-firm mattress that feels more comfortable may in fact be more comfortable. — **JEFFREY REICH**

CME Questions

1. **Which of the following statements is correct?**
   a. Diffusion tensor MRI images grey matter damage in the spinal cord.
   b. Diffusion tensor MRI is useful in the diagnosis of primary lateral sclerosis but not ALS.
   c. Diffusion tensor MRI has high sensitivity and specificity in both primary lateral sclerosis and ALS.
   d. Diffusion tensor MRI is only useful in ALS patients with upper motor neuron signs.

2. **Economy class syndromes may include which of the following?**
   a. Deep-vein thrombosis in lower extremities
   b. Pulmonary embolism
   c. Stroke due to paradoxical embolism
   d. Vertebral artery dissection
   e. All of the above

3. **Which neuropathy has Sjögren syndrome been associated with most commonly?**
   a. Painless sensory ataxic neuropathy
   b. Painful small fiber neuropathy
   c. Painless sensory or sensorimotor polyneuropathy
   d. Mononeuritis multiplex
   e. Combined painful neuropathy with sensory ataxia

4. **Which is the best office test to uncover quadriceps weakness from suspected L3 or L4 radiculopathy?**
   a. The knee-extended manual muscle test
   b. The knee-flexed manual muscle test
   c. The single leg sit-to-stand test
   d. The step-up test
   e. All the above are equally sensitive

Answers: 1(c); 2(e); 3(b); 4(c)

In Future Issues: **Hepatitis C, Cryoglobulins, and Neuropathy**

PHARMACOLOGY WATCH

Vioxx Might Control Postoperative Knee Pain

Oral rofecoxib (Vioxx) may have a role in controlling postoperative pain patients undergoing knee surgery. Researchers in Chicago enrolled 70 patients who were undergoing total knee arthroplasty and randomized them to rofecoxib 50 mg the day prior to surgery, 1-2 hours prior to surgery, and for 5 days postoperatively, then 25 mg daily for another 8 days; or matching placebo at the same times. The main outcome was postsurgical analgesic consumption and pain scores, as well as nausea and vomiting, joint range of motion, sleep disturbance, and patient satisfaction with analgesia and hematologic anticoagulation parameters. Rofecoxib resulted in significantly reduced use of epidural analgesia and in-hospital opioid consumption ($P < .05$). Pain scores were also lower in the rofecoxib group while in the hospital ($P < .001$) as well as 1 week after discharge ($P = .03$). Rofecoxib also resulted in less postoperative nausea, a decrease in sleep disturbance, as well as increased knee flexion at 1 month—including a shorter time in physical therapy to achieve effective joint range of motion. The drug had no effect on warfarin usage or INR levels postoperatively. Interestingly, Buvanendran and colleagues did not include changes in renal function or evidence of GI intolerance in the study analysis. They did conclude however that rofecoxib is effective at reducing postoperative pain and opioid consumption after major orthopedic surgery (*JAMA*. 2003;290:2411-2418).

Echinacea Has No Value for URIs

Just in time for winter, another study showed that *Echinacea* has no value for reducing the duration or severity of upper respiratory tract infections (URIs). The herbal remedy is commonly used worldwide for this indication. In this study of children in the Pacific Northwest, 707 URIs occurred in 407 children over 2 years. Three hundred thirty-seven URIs were randomized to treatment with *Echinacea* while 370 were assigned to placebo. *Echinacea* was begun at the onset of symptoms and continued throughout the infection for maximum of 10 days. Data analysis showed there was no difference in the duration of URIs with *Echinacea* or placebo ($P = .89$), and there was no difference in the overall estimate of severity of URI symptoms ($P = .69$). There was also no statistically significant difference between the 2 groups for peak severity of symptoms, number of days of peak symptoms, number of days of fever, or parental global assessment of severity of URI. Rash occurred during 7.1% of URIs treated with *Echinacea* and 2.7% of those tree with placebo ($P = .008$). The study concludes that *Echinacea* was not effective in treating URI symptoms in patients 2 to 11 years old but was associated with an increase in skin rash (*JAMA*. 2003;290:2824-2830).

Valsartan, Captopril Have Similar Benefits

Valsartan and captopril have similar benefits in patients with myocardial infarction complicated

This supplement was written by William T. Elliott, MD, FACP, Chair, Formulary Committee, Kaiser Permanente, California Division; Assistant Clinical Professor of Medicine, University of California-San Francisco. Telephone: (404) 262-5517. E-mail: robin.mason@ahcpub.com. In order to reveal any potential bias in this publication, we disclose that Dr. Elliott reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study.

by left ventricular systolic dysfunction, heart failure, or both, according to a new study. Previous studies have shown that ACE inhibitors reduce mortality and cardiovascular morbidity in this group, but it was unclear if angiotensin receptor blockers (ARBs) conveyed the same benefit. In this international study, nearly 15,000 patients with myocardial infarction were randomized to valsartan, captopril, or a combination of valsartan and captopril. The primary end point was death from any cause. The median follow-up was just more than 2 years. During that time, the death rate in all 3 groups was remarkably similar (979 of 4909 deaths valsartan, 958 of 4909 deaths captopril, 941 of 4885 deaths combination [hazard ratio valsartan vs captopril 1.0; 97.5% CI, 0.9-1.11; $P = 0.98$], [hazard ratio valsartan and captopril vs captopril, 0.98; 97.5% CI, 0.89-1.09; $P = 0.73$]). The valsartan plus captopril group had the most drug-related adverse events, while in the monotherapy groups valsartan was associated with more hypotension and renal dysfunction, while cough, rash, and taste disturbance were more common with captopril. Pfeffer and associates conclude that valsartan is as effective as captopril in patients with myocardial infarction who are at high risk for cardiovascular events, but combining valsartan with captopril did not offer an advantage (*N Engl J Med*. 2003;349:1893-1906).

In-patients Likely to Continue Lipid Use

In-patients who are started on lipid-lowering therapy following coronary intervention are 3 times more likely to continue on the drugs compared to patients who are started on the same therapy as outpatients. Using data from the EPILOG trial in which patients underwent percutaneous coronary intervention for stable or recently unstable coronary artery disease, 175 patients were discharged from the hospital on lipid-lowering therapy and 1951 were discharged on no lipid-lowering therapy, with the intent to start them on treatment as outpatients. After 6 months of follow-up, 77% of patients who were started in the hospital were still taking lipid-lowering therapy compared with only 25% of those who were discharged without lipid-lowering therapy ($P < .001$). Aronow and colleagues suggest that initiation of lipid-lowering therapy in the hospital is effective strategy to enhance subsequent use of the drugs in these high-risk patients (*Arch Intern Med*. 2003;163:2576-2582).

More on Metformin/Lactic Acidosis

When it comes to the relationship between metformin and lactic acidosis, the emperor may have no cloths. The drug, which has been used to treat type 2 diabetes for more than 40 years, has always carried with it the stigma that it may cause lactic acidosis in at-risk patients. Metformin hydrochloride is a biguanide that is similar in structure to phenformin hydrochloride, which was withdrawn from the market because of a documented risk of lactic acidosis. Metformin increases glucose oxidation without substantially affecting fasting lactate production and peripheral tissues unlike phenformin, and the true rate of metformin-associated lactic acidosis has never been demonstrated. Recently, researchers from Stanford performed a thorough review of the literature on this topic and performed a meta-analysis on 194 studies involving nearly 37,000 patient years in the metformin group and 30,000 patient years in the nonmetformin group. No cases of fatal or nonfatal lactic acidosis were found in either group. Their conclusion is that there is no evidence that metformin therapy is associated with an increased risk of lactic acidosis or with increased lactate levels compared with other antihyperglycemic treatments (*Arch Intern Med*. 2003;163:2594-2602). The study is important because metformin is an effective treatment for type 2 diabetes, and has some unique properties including stabilizing weight gain or even facilitating weight loss. The drug has also recently become multisource (generic) and is affordable for diabetic patients who must pay for their medications.

FDA Notes

The FDA has approved tadalafil (Cialis), Eli Lilly and Icos Corp's entry into the lucrative phosphodiesterase inhibitor market. With the success of sildenafil (Viagra), and newcomer vardenafil (Levitra) already generating huge profits, Cialis is being touted as a longer acting, less expensive alternative for the treatment of erectile dysfunction. The drug, which exerts its effect over 36 hours, has already been dubbed "the weekend drug" in Europe, where it as been available for some time.

Bristol-Myers has received approval to market the first chewable oral contraceptive for women. The product is a new formulation of Ovcon 35 (norethindrone and ethinyl estradiol), which is spearmint flavored and can be chewed or swallowed whole. If chewed than swallowed, the woman should drink a full 8 oz of liquid immediately afterward to make sure the entire dose reaches the stomach. ■