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A monthly survey of developments in neurologic medicine

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INSIDE

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Rivastigmine: Sustained Benefits for Parkinson's Disease Dementia

ABSTRACT & COMMENTARY

By Claire Henchcliffe, MD, DPhil

Assistant Professor, Department of Neurology, Weill Medical College, Cornell University

Dr. Henchcliffe is on the speaker's bureau for GlaxoSmithKline, Teva/Eisai, and Boehringer Ingelheim.

Synopsis: *Rivastigmine demonstrated clinically significant benefits for up to one year in patients with dementia associated with Parkinson's disease.*

Source: Poewe W, et al. Long-Term Benefits of Rivastigmine in Dementia Associated with Parkinson's Disease: An Active Treatment Extension Study. *Mov Disord*. 2006;21:456-461.

THIS 24-WEEK OPEN-LABEL TREATMENT EXTENSION TRIAL AIMED to determine whether 3-12 mg/day of rivastigmine had sustained benefit and continued safety in patients with dementia associated with Parkinson's disease (PDD), following an initial double-blind 24-week trial.[1] Of 541 initial subjects, 433 patients completed the double-blind phase, and 329 of these, plus 5 retrieved dropout subjects, entered the open-label phase. These subjects were of mean age 72.4 ± 6.6 years, mean Parkinson's disease (PD) duration 8.8 ± 5.5 years, mean PDD duration 1.2 ± 1.6 years, mean time from PD diagnosis to first dementia symptom 6.7 ± 4.8 years, baseline Mini Mental State Examination 19.5 ± 3.8 points, and mean Unified Parkinson's Disease Rating Scale (UPDRS) motor score of 32.7 ± 13.4 points. A total of 273/329 patients (81.7%) completed the open-label phase (83.9% from the initial rivastigmine arm, 78.0% from the initial placebo arm). Mean rivastigmine dose at trial completion was 7.9mg/day. For the 176 patients completing 48 weeks of rivastigmine treatment, mean Alzheimer's Disease Assessment Scale cognitive subscale (ADAS-cog) scores were 22.5 ± 9.6 (baseline), 19.3 ± 9.6 (week 24), and 20.4 ± 11.2 (week 48): a mean improvement of 2.0 ± 7.3 (95% CI 0.8-3.1). For the 97 patients initially on placebo followed by open-label rivastigmine, ADAS-cog scores were 23.3 ± 10.3 (baseline), 23.6 ± 11.7 (24 weeks), and 20.8 ± 11.1 (week 48):

a mean improvement of 2.2 ± 8.2, 95% CI 0.5-3.9. Improvements were also observed for secondary outcome measures, including the Alzheimer's Disease Cooperative Study Activities of Daily Living scale. The UPDRS motor score did not change significantly over the course of the study. Overall, 75.4% of patients reported adverse effects in the extension phase, leading to withdrawal in 11.4%. These were most frequently nausea (18.6%), vomiting (11.1%), tremor (6.9%), falls (4.8%), confusional state (5.1%), and hallucinations (4.8%). Parkinsonian symptoms worsened in 18%, mostly with tremor.

COMMENTARY

Dementia in PD is common, with reported prevalence rates of approximately 40%. Patients with PDD have a cholinergic deficit, and the nucleus basalis of Meynert is involved in the underlying pathophysiologic process, providing the rational for symptomatic treatment with a cholinomimetic agent. However, there are multiple processes at play in PDD, including cortical involvement of PD, and Alzheimer Disease-type pathology in some. Rivastigmine is a centrally acting inhibitor of acetylcholinesterase (AChE) and butyrylcholinesterase (BuChE) and is approved by the FDA for the treatment of mild to moderate Alzheimer's dementia (AD). A supplemental new drug application is being sought from the FDA for treatment of PPD.[2] The ADAS-cog is an 11-item, 70 point mental status examination of language, praxis, memory, and orientation. The mean decrease of 2 points over 48 months suggests a modest but significant effect, although use of a scale designed for AD may not be an ideal measure in PDD. The study design of course has some limitations, and there may have been patient selection bias in the second phase: the subset of subjects continuing from the rivastigmine arm of the original 24-week trial had experienced a greater improvement in ADAS-cog than the entire group. Interestingly, the effect of rivastigmine on cognition varied considerably between patients, reflecting clinical practice. This may reflect the heterogeneity of PDD included in this research trial. It emphasizes the need for studies designed to dissect out predictors of drug responses, whether by imaging, pharmacogenetics, or by other means. Nonetheless, the drug was well-tolerated. Therefore, with appropriate discussion of patients' and caregivers' preferences, instituting rivastigmine for symptomatic treatment of PDD may be worthwhile, with the caveat that it is not a golden bullet.

References

1. Emre M, et al. Rivastigmine for Dementia Associated with Parkinson's Disease. *N Engl J Med*. 2004;351: 2509-2518.
2. Food and Drug Administration. Peripheral and Central Nervous System Drugs Advisory Committee; Notice of Meeting for May 17, 2006. Assessed May 9, 2006, at www.fda.gov/OHRMS/DOCKETS/98fr/E6-3021.pdf

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Questions & Comments

Please call **Leslie Hamlin**, Associate Managing Editor, at (404) 262-5416.

A Genetic Cause for Primary Intracerebral Hemorrhage?

ABSTRACT & COMMENTARY

By Matthew E. Fink, MD

Vice Chairman, Professor of Clinical Neurology, Weill Cornell Medical College, Chief, Division of Stroke and Critical Care Neurology, NewYork-Presbyterian Hospital

Dr. Fink reports no financial relationship relevant to this field of study.

Synopsis: *An inherited defect in Type IV collagen, a basement membrane protein, may be a cause of small-vessel disease and primary intracerebral hemorrhage.*

Source: Gould DB, et al. Role of COL4A1 in Small-Vessel Disease and Hemorrhagic Stroke. *N Engl J Med*. 2006:354:1489-1496.

INTRACEREBRAL HEMORRHAGE (ICH) IS THE MOST devastating form of stroke, with a case mortality approaching 50%. While chronic hypertension and advanced age remain the most important risk factors,

up to 40% of cases in people under the age of 50 have no definable etiology. Gould and colleagues have now shed light on a genetic disorder that affects the basement-membrane protein, type IV collagen (COL4A1), in mice and human families with porencephaly, which may predispose to small-vessel disease and intracerebral hemorrhage.

In a previous paper (*Science*. 2005;308:1167), the authors reported that the Col4a1 mutation in mice could cause perinatal hemorrhage and porencephaly in about 20% of newborn pups, and postulated that pressure on the head during birth, in the setting of abnormal small-vessels in the brain, accounted for ICH. In the present study, Gould et al delivered the mutant mice surgically to prevent birth trauma, and demonstrated that intracerebral hemorrhage was prevented at birth in that group compared with naturally born mutant pups, who all had cerebral hemorrhage visible through the skull and skin, with 50% of the pups dying on the day of birth. Among the surgically delivered mutant mice who were allowed to age, many had overt neurological episodes with seizures and hemiparesis, and all had pathological evidence of intracerebral or subarachnoid hemorrhage at autopsy. Hemosiderin-containing lesions were identified in the basal ganglia in 22 animals, and 1 lesion was found in the cortex. Other pathological evidence of small-vessel disease on the mutant mice were found, including retinal vascular tortuosity, defects in the glomerular basement membrane, and microalbuminuria.

In a striking similarity to the mutant mice, Gould et al also describe the phenotypic similarities between Col4a1-mutant mice and a French family with small-vessel disease. All 6 affected members of this family had retinal arterial tortuosity, 2 had infantile hemiparesis, 3 had migraine with aura, and all had neuroimaging that showed diffuse leukoencephalopathy with microbleeds. Two members of the family had fatal intracerebral hemorrhage, one after head trauma, and one while taking anticoagulant medications. DNA sequence analysis of the affected family members showed a G1769A transition in exon 25 of the COL4A1 gene.

COMMENTARY

In a dramatic comparison between a mice-model and a human family, Gould et al have raised the possibility that a genetic disorder affecting basement-membrane collagen can predispose to small-vessel disease and, subsequently, to ICH. This discovery may be one of the missing links in our search for the cause of many cases of intracerebral hemorrhage, some familial, that have eluded diagnosis until now. It also raises the tantalizing idea of a genetic-environmental interaction that may result in ICH after minor trauma or use of anticoagulant medications, and may lead to new approaches for prevention and treatment for ICH.

It also sheds light on a larger group of people with ischemic cerebrovascular disease who are diagnosed with small-vessel disease as a cause of both clinical and silent strokes, as well as progressive dementia. In a companion editorial (*N Engl J Med*. 2006;354:1451), Dr. Greenberg points out that this large and important group of patients have eluded understanding and effective treatment. The traditional view has been that their small-vessel disease (lipohyalinosis) is the result of long-standing hypertension, yet effective treatment of blood pressure seems to do little to stop the progression of this disease, or reverse it. The work by Gould et al has now pointed to Type IV collagen as a new target for our focus and investigation into the causes, prevention, and treatment of small-vessel disease and ICH.

How does this information help us now to treat our patients? We should be more diligent in taking careful family histories, and refer patients for genetic studies when appropriate. We should recognize the attendant risks of minor head injury and use of anticoagulants in patients diagnosed with small-vessel disease, and be particularly aggressive in treating their high blood pressure, since the interaction between weak vessels and high blood pressure may be even more important in this group of patients than we previously thought. ■

Sleep—Sometimes a Test of Survival

ABSTRACT & COMMENTARY

By Charles P. Pollak, MD

Professor, Clinical Neurology, Weill College of Medicine

Dr. Pollak is a stockholder for Merck, and is on the speaker's bureau for Merck.

Synopsis: *Sleep-disordered breathing is a significant risk factor for cardiac arrhythmias and sudden death.*

Source: Mehra R, et al. Association of Nocturnal Arrhythmias with Sleep-disordered Breathing. The Sleep Heart Health Study. *Am J Respir Crit Care Med*. 2006; 173:910-916.

Of all sleep disorders, the ones of greatest concern are those grouped under the rubric sleep-disordered breathing (SDB). They include obstructive sleep apnea, central sleep apnea, sleep hypoventilation,

and related disorders. We have long known that SDB, especially obstructive sleep apnea, is associated with cardiac arrhythmias, including some that are dangerous. However, the extent to which SDB raises the arrhythmia risk has not been known, nor has it been clear whether it is SDB itself or associated characteristics such as age, obesity, and gender that are responsible. Some answers can now be given thanks to a multicenter, longitudinal study of 6441 participants organized in the mid-1990s.

Subjects were divided into those with severe SDB (30 apneas or hypopneas per hour of sleep) and those free of SDB (< 5 apneas or hypopneas). It was postulated that the 228 participants with severe SDB had a higher prevalence of nocturnal cardiac arrhythmias than the 338 who were unaffected. SDB was considered the main risk in this study; correlates included age, BMI, sex, and coronary heart disease.

Arrhythmias were analyzed using ECG interpretation software and were scored as ventricular, ventricular ectopic, or normal beats. Ventricular arrhythmias included premature ventricular contraction, bigeminy, trigeminy, quadrigeminy, nonsustained ventricular tachycardia, or complex ventricular ectopy (nonsustained ventricular tachycardia, bigeminy, trigeminy, or quadrigeminy). Atrial arrhythmias included premature atrial contraction, supraventricular tachycardia, and atrial fibrillation. Conduction delay arrhythmias were coded as first-, second-, and third-degree avioventricular block, intraventricular conduction delay, and sinus pauses lasting at lease 3 seconds.

Arrhythmias that were more common in the SDB group included atrial fibrillation (odds ratio 4.02), nonsustained ventricular tachycardia (OR 3.40), and complex ventricular ectopy (OR 3.40). SDB status was a significant predictor of the number of ventricular ectopic beats per hour (75% higher in those with SDB than those without).

COMMENTARY

Recent studies have shown that the risk of nocturnal sudden death from cardiac causes (as well as stroke) is more than doubled in people with SDB. This study offers a possible explanation. It has also recently been found that increased airway pressure (CPAP) decreases ventricular ectopy in SDB patients, suggesting that the risks associated with nocturnal arrhythmias may be reducible with CPAP. Future systematic investigations of CPAP in such well-defined populations as the one described here are, therefore, anxiously awaited. Meanwhile, the present findings mandate the use of at least one ECG lead in all diagnostic sleep recordings. It also seems desirable that sleep disorders centers secure the ongoing participation of cardiologists, either as team members or consultants. Referring physicians ought to expect polysomnographic reports always to include a section assessing the cardiac rhythm during sleep.

Carotid Artery Stenting and Endarterectomy Compared

ABSTRACT & COMMENTARY

By John C. Caronna, MD

Vice-Chairman, Department of Neurology, Cornell University Medical Center, Professor of Clinical Neurology, NewYork-Presbyterian Hospital

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

Synopsis: *In this retrospective case-control study, carotid stenting with cerebral protection and carotid endarterectomy were not significantly different in early morbidity and mortality.*

Source: Cao P, et al. Outcome of Carotid Stenting Versus Endarterectomy: A Case-Control Study. *Stroke*. 2006;37: 1221-1226.

CAROTID ARTERY ANGIOPLASTY WITH STENTING (CAS) has been accepted by many physicians and most patients as a less invasive alternative to carotid endarterectomy (CEA) for the primary and secondary prevention of stroke related to internal carotid artery (ICA) stenosis. The clinical use of CAS has steadily increased despite initial outcome studies that indicated higher morbidity and mortality rates for CAS than for CEA.[1]

Cao and colleagues report the perioperative and midterm (up to 36 months of follow-up) results of CAS vs CEA in a retrospective, matched case-control study at a single tertiary care hospital in Italy. The primary criterion for treatment was severe ICA stenosis, either symptomatic or asymptomatic. All patients underwent preoperative duplex ultrasound examinations. All patients undergoing CAS had the presence of ICA stenosis confirmed by angiography during the CAS procedure. Patients undergoing CEA had preoperative angiography or CT angiography. Patients with recurrent ICA stenosis, previous cervical radiation therapy, tracheostomy, or ICA stenosis above the C_2 level were excluded from the study.

Of 301 patients who had CAS with cerebral protection, 301 were matched with control patients who had CEA during the same period (2001-2004). Matching was by sex, age, symptoms, and coronary artery disease.

Table 1

Complications at 30 Days

	Patients (CAS) n = 301	Patients (CAS) %	Patients (CEA) n = 301	Patients (CEA) %	P	OR
Disabling Stroke/Death*	8	2.6	4	1.3	NS	2
Any Stroke	24	7.9	7	2.3	0.001	4
Myocardial Infarction	2	0.6	5	1.6	NS	0.4
TIA**	19	6.3	3	1.0	0.0004	9.5
Local Complications	13	4.3	10	3.3	NS	1.3

(After Cao et al.)

* Treated patients

** Includes intention-to-treat patients

Outcome measures were stroke, death, cardiac events, and local complications. Intraprocedure CAS complications were divided into 3 phases:

1) During the passage of the aortic arch and cannulation of the ICA;

2) The crossing of the lesion phase including placement of the cerebral protection device (CPD); and

3) The stent-ballooning procedure including recovery of the CPD.

There was no evidence of a statistically significant increase in the risk of disabling stroke and death in CAS patients compared with CEA controls (*see Table 1*). The risk of any stroke, however, favored CEA over CAS. Eight disabling strokes (2 fatal) occurred in the CAS group. Four were due to massive embolization during phase one. The remaining 4 strokes occurred during phase 3. Of 16 nondisabling strokes in CAS patients, one occurred during phase one, one during phase 3, 10 within the first 24 hours after CAS, and 4 after 24 hours. The majority of TIAs (18/19) occurred during phase 3 of CAS. Bradycardia or hypotension occurred during the procedure in 34% of CAS patients, despite the use of atropine.

At a mean follow-up of 18 months (range, 3-48 months), there was no significant difference in the rate of restenoses in the CAS group (n = 4, 1.3%) vs the CEA group (n = 10, 3.3%).

COMMENTARY

Although the study is a retrospective analysis of a nonrandomized population, Cao et al's observations provide useful insights into the intraprocedural stroke risk for patients undergoing CAS. Notable, too, was the presence of a learning curve for technical expertise in performing CAS. The first 100 CAS patients had a higher stroke rate than later CAS patients. Therefore, if the first 100 CAS patients are excluded from outcome analysis, then the last 201 CAS patients did not have a stroke risk significantly different from the corresponding 201 CEA-matched controls.

At present, it is not possible to exclude a difference favoring one treatment over the other. Nevertheless, given the appropriate technical expertise and experience, an interventionalist performing CAS can expect outcomes identical to those achieved by the surgeon performing CEA.

Reference

1. Endovascular versus Surgical Treatment in Patients with Carotid Stenosis in the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS): A Randomised Trial. *Lancet*. 2001;357:1729-1737.

Evaluation of Neuropathy in Diabetes

ABSTRACT & COMMENTARY

By Norman Latov, MD, PhD

Professor of Neurology and Neuroscience, Director, Peripheral Neuropathy Center, Weill Medical College of Cornell University

Dr. Latov is a consultant for Quest Diagnostics and Talecris Biotherapeutics, Inc., is a stockholder for Therapath LLC, and has royalties in Athena Diagnostics.

Synopsis: *Patients with diabetes that present with neuropathy need to be evaluated for other potential causes of neuropathy, in addition to the diabetes.*

Source: Gorson KC, Ropper AH. Additional Causes for Distal Sensory Polyneuropathy in Diabetic Patients. *J Neurol Neurosurg Psychiatry*. 2006;77:354-358.

In a retrospective study of approximately 100 patients with distal symmetric neuropathy and diabetes

that were evaluated at an academic referral center, 53% had other potential causes of neuropathy, with 25% having more than one additional cause. Other causes for neuropathy identified in this patient cohort, included neurotoxic medications, alcohol abuse, renal disease, monoclonal gammopathy, chronic inflammatory demyelinating polyneuropathy (CIDP), and deficiencies of vitamins B_{12}, B_1 or B_6 Cao et al conclude that patients with diabetes who present with neuropathy cannot be presumed to have diabetes as the only cause of the neuropathy, and should be evaluated for other potential causes.

COMMENTARY

When evaluating a patient with diabetes and neuropathy, it is common to presume that the neuropathy is diabetic and that no further testing needs be done. However, as patients with diabetes can also develop other maladies, a certain percentage would be expected to have other causes for neuropathy, similarly to those without diabetes. In addition, diabetes can predispose to other conditions that can cause or contribute to the neuropathy, such as B_{12} deficiency resulting from metformin therapy or atrophic gastritis, other nutritional deficiencies associated with malabsorption, or CIDP. The figure of 53% may be higher than that seen in routine practice, possibly due to referral bias at a tertiary academic center, but the message still holds. Patients with diabetes need to be evaluated for other potential causes of neuropathy, particularly if the presentation is atypical or the neuropathy progresses despite optimal glycemic control.

Migraine: More Than Just a Headache!

ABSTRACT & COMMENTARY

By Dara G. Jamieson, MD

Associate Professor, Clinical Neurology, Weill Medical College of Cornell University

Dr. Jamieson is a consultant for Boehringer Ingelheim and Merck, and is on the speaker's bureau for Boehringer Ingelheim, Merck, Ortho-McNeil, and Pfizer.

Synopsis: *Upper abdominal pain, without anatomic explanation, occurs in over 80% of adult patients with migraine, and may be part of the migraine syndrome.*

Source: Kurth T, et al. Prevalence of Unexplained Upper Abdominal Symptoms in Patients with Migraine. *Cephalalgia*. 2006;26:506-510.

Gastrointestinal symptoms are prominent in children with migraine, and are associated with both headaches and with childhood periodic syndromes that are commonly precursors of migraine. Cyclic nausea and vomiting without signs of gastrointestinal disease occur in schoolchildren as a migraine precursor. Children may have abdominal migraine with recurrent attacks of abdominal pain associated with anorexia, nausea, and vomiting. There is an increased incidence of maternal migraine history in children with abdominal migraine, reinforcing the position that migraine and abdominal migraine may have a common pathogenesis.

Nausea and vomiting, part of the ICHD-2 diagnostic criteria for migraine, are arguably the most socially and physically disabling symptoms for adult patients with migraine. Occasionally, the prominence of gastrointestinal symptoms may be greater than head pain. These symptoms are rarely seen in patients with episodic or chronic tension-type headaches or other primary headache types. (Lipton RB, et al. Classification of Primary Headaches. *Neurology*. 2004;63:427-435).

Adults with migraine may have co-morbid gastrointestinal disorders including irritable bowel syndrome, but the association between abdominal pain and migraine, well recognized in children, is less established in an adult migraine population. The aim of this paper was to survey the prevalence of idiopathic dyspeptic symptoms in patients with migraine, and to compare the prevalence of upper abdominal pain to that of a control population of healthy non-migraineurs. During a 6-week period, 99 consecutive patients were recruited from a headache clinic at the University Hospital, Essen. They were diagnosed with migraine with or without aura by the 1988 International Headache Society Criteria. The control group was made up of 488 apparently healthy blood donors without reported migraine or headaches. A validated Bowel Disease Questionnaire was administered to both groups to evaluate gastrointestinal tract symptoms. Patients or controls who reported upper abdominal pain occurring more than 6 times in the past year were considered to have frequent dyspepsia. Other potential risk factors for gastrointestinal symptoms, including smoking, high alcohol consumption, and analgesic use, were also assessed.

As compared to the healthy blood donors, migraine patients were more likely to be female (76% vs 34%) and older (mean age, 41.5 years vs 34.1 years) with greater analgesic use. Upper abdominal pain was seen in 80.9% of migraine patients and 37.5% of healthy blood donors. After adjusting for potential confounding conditions, the prevalence odds ratio of idiopathic upper abdominal pain symptoms in migraine patients was increased by 170% compared to healthy blood donors (OR 2.7; 95% CI 1.2, 6.1; $P < 0.001$). There was no association between the dose of analgesic and the severity of gastrointestinal

symptoms. Even correcting for aspirin and other analgesics use, the prevalence of dyspepsia was increased among migraineurs when compared with controls.

Gorson and colleagues concluded that the prevalence of upper abdominal pain symptoms is increased in a population of migraine patients, even adjusting for confounding conditions or analgesic use. Gorson et al were not able to correlate upper abdominal pain symptoms with migraine type or severity but, because this was a referral population, these patients may have had more severe migraines.

COMMENTARY

There may be both clinical and mechanistic overlap between dyspepsia and migraine. Meal-induced gastric hypersensitivity is seen in both dyspeptic individuals and migraineurs. Vagal dysfunction may come into play with both migraine and dyspepsia, and there are shared neuropeptides. Calcitonin gene-related peptide (CGRP) is increased during the migraine attack, and plays an important role in the neuro-inflammatory pathogenesis of migraine. CGRP may play a role in visceral afferent nerve sensitization of gastrointestinal origin; although its role in dyspepsia is unclear. Upper abdominal symptoms should be added to the growing list of symptoms experienced by migraineurs, indicating that migraine is more than just a headache.

Electrodiagnostic Study of Anorectal Dysfunction

ABSTRACT & COMMENTARY

By Michael Rubin, MD

Professor of Clinical Neurology, NewYork-Presbyterian Hospital, Cornell Campus

Dr. Rubin is on the speaker's bureau for Athena Diagnostics, and does research for Pfizer and Merck.

Synopsis: *Future research will demonstrate whether these tests can also document and monitor the benefit of specific therapeutic interventions.*

Source: Lefaucheur JP. Neurophysiological Testing in Anorectal Disorders. *Muscle Nerve*. 2006;33:324-333.

ELECTRODIAGNOSTIC EXAMINATION OF THE ANOGENITAL region may be unpleasant and awkward for both patient and physician, but valuable information, of both diagnostic and prognostic value, can be garnered by a variety of techniques in the work-up of suspected peripheral or central disorders of anorectal dysfunction.

Electromyography (EMG) of the external, striated, anal sphincter muscle is performed by needling the 4 quadrants of the muscle. Automated computerized programs have enhanced the diagnostic sensitivity of this test, and guidelines have been standardized to quantify the findings (*Clin Neurophysiol*. 2000;111;2200-2207). At rest, the normal sphincter demonstrates tonic activity, whereas active denervation may be documented by the presence of fibrillation potentials and high frequency repetitive discharges. Chronic denervation with reinnervation is evidenced by a reduced interference pattern comprising large amplitude, long duration, motor unit potentials. Amyotrophic lateral sclerosis generally spares the external anal sphincter, whereas, it is involved in multiple system atrophy (MSA). Controversy exists as to whether its involvement differentiates MSA (affected) from Parkinson's disease (spared). EMG of the internal anal sphincter muscle remains predominantly a research tool. Surface EMG, which would significantly facilitate study of this region for both examiner and examinee, has yet to achieve the sensitivity of needle EMG. When combined with anorectal manometry, however, surface EMG has demonstrable utility, exhibiting abnormal patterns of rectal muscle activation, whether increased, explaining chronic constipation, or deceased, explaining fecal incontinence.

Single fiber EMG (SFEMG) can objectively document the presence of reinnervation within the anal sphincter muscle by measuring fiber density, which increases in the chronic phase of neurogenic injury, analogous to fiber type grouping. It remains infrequently used. SFEMG measurement of jitter, which increases in neuromuscular junction disorders such as myasthenia, is of little utility in anogenital disorders, given that they are spared in these conditions.

Transrectal electrical stimulation of the pudendal nerve, performed by insertion of the index finger into the rectum while wrapped in a glove attached to a St. Mark's electrode, allows for measurement of the terminal motor latency (TML) of this nerve. Reportedly useful in predicting whether surgical repair of perineal tears will benefit the (usually) postpartum patient, the technique remains less sensitive than needle EMG for documenting anal sphincter denervation. Questions of the true validity of the test have also been raised based on the surprisingly short latency values obtained using the St. Mark's electrode. Muscle artifact may seriously interfere with accurate recording, values vary with age, and findings do not correlate with anorectal manometry. TML recordings by this technique are, thus, of questionable value. Sacral magnetic stimulation of the sacral roots at the sacral foramina, to evoke anal

sphincter compound muscle action potentials, analogous to routine motor nerve conduction studies, may offer a viable alternative. Less painful and less uncomfortable, magnetic stimulation also allows for simultaneous study of both central and peripheral sphincter motor pathways.

Transcranial magnetic stimulation of the motor cortex, with recording of external anal sphincter evoked motor responses, permits assessment of central motor pathway conduction times and excitability of cortical motor circuitry. To date, the clinical relevance of these studies remains to be established.

Reliable somatosensory evoked responses (SEP) may be elicited by stimulating the rectal wall, anal canal, or anal verge, while recording over the cortex, but stimulation of the dorsal nerve of the clitoris and penis are more sensitive. Yet, small diameter spinothalamic pathways are not studied by SEP, and further research to overcome this limitation is ongoing.

By electrically stimulating the anal mucosa in a graded, stepped manner, and asking the patient to report when (s)he feels the stimulus, it is possible to quantify the patient's perception threshold, so-called quantitative sensory threshold testing. Reproducible, accurate, and, when abnormal, associated with rectal incontinence, it is nonspecific, altered by age and feces in the anal canal, and does not correspond to natural stimuli. Thermal sensory threshold testing can overcome some of these drawbacks but may not correlate with anal incontinence. Neither method differentiates central from peripheral causes, and both depend on patient cooperation, making them, in this sense, subjective.

Sacral anal reflex latency measurements are age and sex dependant, but have been obtained by electrically stimulating either the pudendal nerve (dorsal nerve of penis or clitoris) or the perianal region, and recording from both the bulbocavernosus muscle and external anal sphincter. Reproducibility in the latter is poor, and onset latency is difficult to measure accurately. Findings cannot differentiate central from peripheral causes.

Sympathetic skin responses (SSR) may be obtained by electrically stimulating the face or arm and recording from the perineal region. Central from peripheral causes of anal dysfunction may then be differentiated, by comparing the perineal response to palmar and plantar SSR recordings, but SSRs lack sensitivity and reproducibility.

Electrophysiologic testing of anorectal dysfunction is an extension of the clinical examination. Various available tests complement anorectal manometry and each other. Future research will demonstrate whether these tests can also document and monitor the benefit of specific therapeutic interventions. ■

COMMENTARY

Even after correct diagnosis, anorectal disorders can remain therapeutically challenging. Botulinum toxin, useful in so many others areas of neurology, has recently been used to treat spasticity of the anal sphincter, as well as paradoxical puborectal syndrome, a disorder where there is insufficient relaxation of the sphincters with straining on defecation. Anal fissure can also be cured with Botox. Where will they put it next? ■

CME Questions

15. Which of the following statements is TRUE?
1) Small-vessel disease is a rare cause of ischemic stroke
2) Hypertension is a major risk factor for intracerebral hemorrhage
3) Traumatic brain injury is not a common cause for ICH
4) We have effective treatments for small-vessel disease

16. The following statements are TRUE regarding sleep-disordered breathing (SDB).
1) SDB increases the risk of stroke
2) SDB increases the risk of serious cardiac arrhythmias
3) SDB increases the risk of sudden death
4) All of the above

17. Disabling strokes associated with carotid artery angioplasty with stenting occur most frequently during:
A) Phase one, the passage of the catheter across the aortic arch
B) Phase two, the placement of the cerebral protecting device
C) Phase three, the stent -ballooning procedure
D) Phases one and three
E) Phases one and two

Answers: 15. (b); 16. (d); 17. (d)

CME Objectives

The objectives of *Neurology Alert* are:

• To present current scientific data regarding diagnosis and treatment of neurological disease, including stroke, Alzheimer's disease, transient ischemic attack, and coma;

• To discuss the pathogenesis and treatment of pain;

• To present basic science lessons in brain function;

• To discuss information regarding new drugs for commonly diagnosed diseases and new uses for traditional drugs; and

• To discuss nonclinical issues of importance to neurologists, such as the right to die and the physician's legal obligation to patients with terminal illness. ■

In Future Issues:

The CHARISMA Study

PHARMACOLOGY WATCH

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

Gastric Acid Secretion and the Absorption of Thyroxine

The absorption of thyroxine is strongly influenced by stomach acidity, according to new study. Researchers from Italy looked at 248 patients with multinodular goiter who were treated with thyroxine with a goal thyrotropin (TSH) level of 0.05 to 0.20 mU/L. Of these patients, 53 had *Helicobacter pylori* related gastritis and 60 had atrophic gastritis of the stomach. The reference group comprised 135 patients with multinodular goiter and no gastric disorders. The study also included 11 patients who were infected with *H. pylori* during the study and 10 patients who were treated with omeprazole and had no gastroesophageal reflux. Patients with *H. pylori*-related gastritis, atrophic gastritis, or both had a daily requirement of thyroxine that was 22-34% higher than the reference group. In the 11 patients who became infected with age by lower *H. pylori* during the study, thyrotropin levels increased significantly (P = 0 .002), an effect that was nearly reversed with eradication of *H. pylori*. Treatment with omeprazole also increased serum thyrotropin levels (median 1.70mU/L increase in thyrotropin; P = 0.002), requiring a 37% increase in thyroxine dose.

The authors conclude that normal gastric acid secretion is necessary for effective absorption of thyroxine, and factors that impair acid secretion including atrophic gastritis, *H. pylori* gastritis, and treatment with omeprazole require increased doses of thyroxine (*N Engl J Med*. 2006;354:1787-1795). This study has important implications, given millions of patients who take thyroxine, the frequency of *H. pylori* infections in this country, and frequency of use of OTC and prescription proton pump inhibitors.

Can Plavix Add to the Efficacy of Aspirin?

Does clopidogrel (Plavix) add to the efficacy of low aspirin in patients with vascular disease? No, according to new study published in the April 20th *New England Journal of Medicine*. CHARISMA (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance) is a multinational study which randomized 15,603 patients with either clinically evident cardiovascular disease or multiple risk factors to receive clopidogrel (75 mg/d) plus low-dose aspirin (75-162 mg/d) or placebo plus low-dose aspirin for median of 28 months. The efficacy primary end point was a composite of myocardial infarction, stroke, or death from cardiovascular causes. The rate of this end point was 6.8% with the combined drug treatment versus 7.3% with aspirin plus placebo (P = 0.22) for the subgroup of patients with multiple risk factors, the rate of the primary end point was lower for aspirin plus placebo (5.5% aspirin plus placebo versus 6.6% aspirin plus clopidogrel; P = 0.20) and the rate of death from cardiovascular causes was also higher with clopidogrel plus aspirin vs aspirin plus placebo (3.9% versus 2.2%; P = 0.01).

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. 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. Questions and comments, call: (404) 262-5416. E-mail: leslie.hamlin@thomson.com.

In the subgroup with clinically evident atherothrombosis, there was a slight benefit for aspirin plus clopidogrel (6.9% versus 7.9%, P = 0.46).

The authors conclude that overall, clopidogrel plus aspirin was not significantly more effective than aspirin alone in reducing the rate of myocardial infarction, stroke, or death from cardiovascular disease (*N Engl J Med*. 2006;354:1706-1717). An accompanying editorial acknowledges that there were many subgroups within CHARISMA that showed varying outcomes with clopidogrel plus aspirin, but cautions against differentiating patients along the lines used in the study. The editorialists find that "these data showed no significant benefit associated with long-term clopidogrel therapy in addition to aspirin." (*N Engl J Med*. 2006;354:1744-1746).

Prevention of Hypertension?

Prehypertension is defined as blood pressure in the range of 120 to 139 mm Hg systolic or 80 to 89 mm Hg diastolic. Since JNC-VII, there has been increased interest in prehypertension since it has been associated with excess morbidity and deaths from cardiovascular causes. A new study suggests that pharmacologic intervention in patients with prehypertension may help prevent progression to hypertension. The Trial of Preventing Hypertension (TROPHY) looked at 809 patients with prehypertension. A total of 409 patients were randomly assigned to candesartan or placebo for 2 years, followed by 2 years of placebo for both groups. When a study participant reached the study end point of stage I hypertension, they were treated with antihypertensive agents.

Both treatment and placebo groups were instructed in lifestyle changes to reduce blood pressure throughout the trial. During the first 2 years, hypertension developed in 154 participants in the placebo group and 53 in a candesartan group ($P < 0.001$). After 4 years, hypertension had developed in 240 participants in the placebo group and 208 in the candesartan group (relative risk reduction 15.6%; $P < 0.007$). Serious adverse events were slightly higher in the placebo group.

The authors conclude that treatment of prehypertension with candesartan was well-tolerated and reduced the risk of incident hypertension during the study period (*N Engl J Med*. 2006;354:1685-1697). In an accompanying editorial, it is pointed out the prehypertension is present in the about 70 million Americans, and is estimated to decrease average life expectancy by as much as 5 years. Despite this, the author urges caution in recommending wholesale treatment of all patients with prehypertension until more information is available on which drugs are most effective and the best duration of therapy. In the meantime, lifestyle changes, which benefit all risk factors, should be recommended for all patients with prehypertension (*N Engl J Med*. 2006;354:1742-1744).

Estrogen Alternatives

Since publication of the Women's Health Initiative (WHI), many postmenopausal women have discontinued estrogen, and most newly menopausal women are considering alternatives. A recently published paper systematically reviews clinical trials of nonhormonal treatments for hot flashes. More than 4000 studies were considered. Forty-three trials met inclusion criteria, including 10 trials of antidepressants, 10 trials of clonidine, 6 trials of other medications, and 17 trials of isoflavone extracts. In the antidepressant group, both selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) were effective in decreasing the daily number of hot flashes compared to placebo (mean difference -1.13; 95% CI, -1.70 to -0.57). Clonidine was also somewhat effective (-0.95; 95% CI, -1.44 to - 0.47), as was gabapentin (-2.05; 95% CI, -2.80 to -1.30). Red clover isoflavone extracts were not effective, and mixed soy isoflavones had mixed results. The authors conclude that SSRIs, SNRIs, clonidine, and gabapentin provide evidence for some efficacy; however, none are as effective as estrogen (*JAMA*. 2006;295:2057-2071).

FDA Actions

In April, the FDA issued a statement rejecting the medical use of marijuana, citing past evaluations by several US government agencies that showed that "no animal or human data supported the safety or efficacy of marijuana for general medical use." The statement supports the Drug Enforcement Agency's approach to treating all use of marijuana as a criminal act.

Zanamivir (Relenza), GlaxoSmithKline's inhaled anti-influenza drug has received a new indication for prophylaxis of influenza in patients age 5 years and older. The approval was based on 4 large-scale, placebo-controlled trials which showed that the drug was effective in reducing spread of influenza among household members and in community outbreaks. ■