AMERICAN HEALTH CONSULTANTS®

Providing Evidence-Based Clinical Information for 19 Years

NEUROLOGY ALERT®

A monthly survey of developments in neurologic medicine

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

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

Is MCI Really Early AD?

ABSTRACT & COMMENTARY

Source: Morris JC, et al. Mild cognitive impairment represents early-stage Alzheimer's disease. *Arch Neurol.* 2001;58:397-405.

Persons having mild cognitive impairment (mci) display deficits that are greater than expected for their age, but less than would be considered diagnostic of dementia. MCI is considered a state of increased risk for Alzheimer's disease (AD), to the extent that persons with MCI develop AD at a higher rate than comparably aged individuals without cognitive impairments. The issue of whether MCI actually represents an early, transitional stage of AD in all cases is a hotly debated topic.

Researchers at Washington University (St. Louis) have added fuel to this fire by carrying out a nearly decade-long observational study of individuals with MCI that included careful clinical-neuropathological correlations. The study used the Clinical Dementia Rating Scale (CDR). MCI is taken to be equivalent to a CDR score of 0.5, while normal cognition is rated as 0 and mild dementia as 1. A unique feature of the Washington University study was the further stratification of CDR 0.5 group into 3 subcategories based on the rater's confidence that the condition was an early manifestation of dementia of the AD type (DAT). When the rater had the highest confidence of likely progression to AD, the participants were scored as 0.5/DAT. Moderate confidence of progression merited a 0.5/incipient DAT rating, while lowest confidence led to a 0.5/uncertain dementia label. In general, patients with memory loss as part of the primary presentation and greater degree of initial impairment were more likely to be placed in the 0.5/DAT group.

Morris and colleagues found that all of the persons given a designation of 0.5/DAT went on to become demented over 9.5 years. Approximately 61% of MCI patients developed dementia in 5 years, while only 35.7% of the 0.5/incipient DAT and 19.9% of the 0.5/uncertain group went on to develop clear-cut dementia over that time. Thus, the rate of progression of MCI to dementia depended on the level of impairment at presentation. A total of 25 MCI patients came to autopsy, and 21 (84%) were found to have AD. Morris et al concluded that there is sufficient correlation between the state of MCI and subsequent autopsy findings of AD to indicate that MCI actually represents an early stage of AD.

Volume 19 • Number 9 • May 2001 • Pages 65-74

INSIDE

Severe Parkinson's disease **page 66**

COX-2 inhibitors **page 67**

Chronic fatigue and vasovagal faints **page 69**

Alternative treatments for tics **page 70**

Limb-girdle dystrophy **page 71**

COMMENTARY

This study makes the important observation that persons given a CDR rating of 0.5 and the clinical designation of MCI do not all share the same risk level of developing AD. MCI can represent a possible transition state to dementia, but it is heterogenous in terms of the degree of impairment on presentation and the cognitive domains initially involved. It appears that the previously reported rates of conversion from MCI to AD of 10-15% per year are most applicable to individuals with slightly more advanced cognitive decline and memory loss as an initial feature of their presentation.

In clinical practice, it can be difficult to reliably identify MCI patients without using the kind of detailed assessment tools used in clinical research studies. It would be even more difficult for practicing neurologists to draw distinctions among subgroups of MCI patients as was done in this study. This emphasizes the need for caution in applying the MCI construct outside of a research context. Persons already labeled as having MCI may need reassurance that their risk of developing AD may not be as high as some sources have previously indicated.

This study and others like it prove that it is possible to identify a select population of mildly impaired persons who have a high likelihood of developing AD within a few years. It remains to be seen whether the broader group of patients in the state currently defined as MCI are all suffering from an early stage of AD. **—norman r. relkin**

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

VICE PRESIDENT/
GROUP PUBLISHER: Donald R. Johnston.
EDITORIAL GROUP HEAD: Glen Harris.
MANAGING EDITOR: Robin Mason.
ASSOCIATE MANAGING EDITOR: Neill Larmore.
MARKETING PRODUCT MANAGER: Schandale Kornegay.
GST Registration Number: R128870672.
Periodical postage paid at Atlanta, GA.
POSTMASTER: Send address changes to ***Neurology Alert,*** P.O. Box 740059, Atlanta, GA 30374.

Back issues: $37. Missing issues will be fulfilled by Customer Service free of charge when contacted within one month of the missing issue's date.

This is an educational publication designed to present scientific information and opinion to health professionals, to stimulate thought, and further investigation. It does not provide advice regarding medical diagnosis or treatment for any individual case. It is not intended for use by the layman.

AMERICAN HEALTH CONSULTANTS™
THOMSON HEALTHCARE

Subscriber Information

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

Subscription Prices

United States
$269 per year.
Multiple Copies
2-9 additional copies: $197. 10-20 copies: $175.
Canada
Add GST and $30 shipping.
Elsewhere
Add $30 shipping.

Accreditation

American Health Consultants (AHC) designates this continuing medical education (CME) activity for up to 20 hours of Category 1 credit toward the AMA Physician's Recognition Award.

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.

Questions & Comments

Please call **Neill Larmore**, Associate Managing Editor, at (404) 262-5480 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. Rubin serves on the speaker's bureau of Athena and does research for Asta Medica. Dr. Plum, Dr. Caronna, and Dr. Frucht report no consultant, stockholder, speaker's bureau, research, or other relationships related to this field of study.

Embryonic Dopamine Neurons for Severe Parkinson's Disease

ABSTRACT & COMMENTARY

Source: Freed CR, et al. Transplantation of embryonic dopamine neurons for severe Parkinson's disease. *N Engl J Med.* 2001;344:710-719.

For more than 2 decades, transplants of human embryonic dopamine neurons have been performed in patients with Parkinson's disease in an attempt to treat the symptoms or halt the progression of the disease. Although there are numerous reports of patients who have benefited from the procedure, these results must be interpreted with caution. Prior to the present study, there were no double-blind trials of fetal tissue transplantation in Parkinson's disease, and the number of patients reported in open-label series was small. This study by Freed and colleagues generated tremendous interest in the scientific community and in the lay press. Such a careful, double-blind, controlled study of fetal tissue transplantation in Parkinson's disease will not likely be repeated. It is, thus, worthwhile to consider this landmark report in some detail.

The study was performed as a collaborative effort between Columbia-Presbyterian Medical Center, the University of Colorado School of Medicine, and North Shore University Hospital. Patients were eligible to enroll if they had Parkinson's disease of at least 7 years duration, with good response to levodopa and no evidence of dementia or hallucinations. They were evaluated before surgery and at 4-, 8-, and 12-month intervals after surgery. Evaluations included examinations in the on and off state using standard clinical rating scales for Parkinson's disease and quantitative 18-flurodopa PET scanning (which measures the presynaptic nigrostriatal dopaminergic pathway). The primary outcome variable of the study was the change in patients' perception of their global functioning, as measured by a quantitative scale.

Patients were randomly assigned to receive either placebo or active transplant. In the active group, 4 human embryonic mesencephalic extracts were implanted bilaterally into the putamen using a stereotactic approach through frontal burr holes. Two extracts were implanted per side, extending the full anterior-posterior dimension of the putamen. Physicians, nurses, and PET scanning

technicians who cared for patients were unaware of their assignment to either active transplant or placebo. Only the statistician, safety monitoring board, and neurosurgeons in Colorado were aware of the assignment. Patients who underwent placebo surgery had burr holes drilled in the skull, but the dura was not pierced. On completion of the double-blind phase, all patients were offered the option of active transplant; 14 of 20 patients in the placebo arm underwent the procedure.

The study yielded many important results. Rigidity and bradykinesia, as measured by clinical rating scales, improved after transplantation. Patients younger than 60 years had modest improvements on global rating, whereas those older than 60 years did not improve. However, there was no statistically significant difference in the primary outcome variable between patients who received active transplants and those who received placebo surgery.

A total of 16 out of 19 patients who underwent active transplantation experienced statistically significant increases in 18-flurodopa uptake in the putamen, indicating that embryonic dopaminergic cells engrafted successfully. There was no difference in the extent of re-innervation of the putamen between older and younger patients. Two patients died during the study—1 in an automobile accident and 1 of a myocardial infarction. In the latter case, death occurred 3 years after transplantation. Examination of this patient's brain showed dopamine-neuron outgrowth extending the entire length and breadth of the putamen. These data support the assertion that the transplant technique was sufficient to fully re-innervate the striatum in the majority of patients.

Nine serious adverse events occurred in the transplant group; most were judged unrelated to transplantation. More concerning, of 33 patients who ultimately received transplants, 5 developed involuntary dystonic and dyskinetic movements; these persisted despite reduction or even elimination of levodopa. In several patients, involuntary movements were severe enough to pose a significant risk to their ability to perform activities of daily living, including swallowing. Based on this information, 6 patients in the sham group who had yet to decide whether to undergo the active procedure were advised against it.

COMMENTARY

Few neurologists escaped the news coverage announcing the results of the transplant study. The study generated considerable interest for several reasons. Many people raised ethical concerns over the use of a placebo surgical arm. In retrospect, this was critical to the power of the study, as 2 patients in the placebo arm reported substantial benefits at 1-year follow-up prior to unblinding. A full discussion of the political, ethical, and moral consequences of the use of fetal tissue is beyond the scope of this review.

Most lay reports summarizing this transplant study called it a resounding failure. This is an unfortunate distortion of the results. As proof of principle, this study showed that fetal dopaminergic cells successfully engraft into both older and younger patients, and that re-innervation of the striatum is probably complete by three years after transplant. Unfortunately, dopaminergic re-innervation of the striatum using this technique is not adequate to produce a clinically significant benefit in younger patients. The technique does not benefit patients older than 60 years at all. One explanation for this result is that neurodegenerative changes downstream from the nigrostriatal pathway contribute significantly to patients' deficits in advanced Parkinson's disease. In a sense, this is not a surprise, as these patients often have incomplete response to treatment with levodopa.

The most unexpected and concerning result of this study was the development of disabling dyskinesias in younger patients who were successfully engrafted. The fact that dyskinesias persisted after levodopa was eliminated proves that the engrafted cells generated them. For these patients, such "run-away dyskinesias" present a terrible problem, as they cannot be terminated by medication adjustments and they may be very resistant to treatment. Presumably, these dyskinesias result from inappropriate or aberrant re-innervation of the striatum. Until the mechanisms responsible for generating these involuntary movements are fully understood, it would be hard to recommend transplantation of any dopaminergic cell line in humans as a treatment for Parkinson's disease. **—steven frucht**

Cox-2 Inhibitors Linked to CNS Pain Pathways

ABSTRACT & COMMENTARY

Source: Samad TA, et al. Interleukin-1beta-mediated induction of Cox-2 in the CNS contributes to inflammatory pain hypersensitivity. *Nature.* 2001;410:471-475.

Cyclooxygenase (cox)-2 inhibitors such as celecoxib (Celebrex) and rofecoxib (Vioxx) have become popular drugs not only for the treatment of arthritis, but for a wide range of pain syndromes. The data of Samad and colleagues indicate that this clinical practice may have a basis in science. In addition to inhibition of the peripheral production of prostaglandins,

suppression of Cox-2 within the spinal cord and brain may explain the potential efficacy of these agents.

Traditional NSAIDS act nonspecifically on both isoforms of Cox: Cox-1, which is expressed constitutively in all tissues including the gastric mucosa and kidney; and Cox-2, which is specifically induced at the site of inflammation. Selectivity for Cox-2, therefore, maximizes the therapeutic benefit of these drugs while avoiding side effects such as gastrointestinal bleeding. Cox enzyme activation promotes the conversion of arachidonic acid to prostaglandins. In the peripheral nerve terminals, prostaglandins then activate protein kinases, which lead to excitation of sodium channels and reduction of pain thresholds. As Samad et al demonstrate, Cox-2 and prostaglandin activity also contribute to hypersensitivity of pain pathways in the spinal cord and brain.

Using a well-accepted rat model of hindpaw inflammation induced by injection of complete Freund's adjuvant (CFA), Cox-2 mRNA was measured in the lumbar spinal cord at the L4-5 segments. There was a 16-fold increase in mRNA expression at 6 hours, ipsilateral to the stimulus. Bilateral Cox-2 activation was observed extending to 24 hours after the onset of pain. Increases in Cox-2 mRNA expression were also observed in the cervical spinal cord, pons, ventral midbrain, and hypothalamus; a large 12-fold sustained increase occurred in the thalamus. This central Cox-2 induction was accompanied by greater than 80-fold increase in prostaglandin E2 (PGE2) concentration in the CSF.

Samad et al test 2 possible hypotheses for the mechanism of Cox-2 induction in the CNS: sensory inflow from nerve fibers innervating the inflamed hindlimb or activation by circulating pro-inflammatory cytokines. The first of these possibilities was tested using an injection of bupivacaine to induce complete sensory and motor blockade of the sciatic nerve. Samad et al demonstrate that Cox-2 induction and PGE2 production are reduced but not eliminated. Interestingly, C-fiber activation using an electrical stimulus induced Cox but at much lower levels than did inflammation. As Samad et al contend, these data make a transsynaptic mechanism much less likely and point to an inflammation-related, likely humoral, mechanism of Cox expression. A prime candidate for this is the cytokine IL-1•, which is upregulated more than 10,000-fold after the hindpaw is inflamed.

Receptors for IL-1• are highly expressed in the spinal cord, particularly Rexed laminae.[1-3] Interestingly, exogenous administration of IL-1• by an intrathecal route produced 20- to 30-fold more Cox activation than did an equipotent intravenous dosage. Endogenous IL-1• is likely produced not only at the site of peripheral injury but also by glial or neuronal cells within the spinal cord itself. Given that IL-1• levels are not found to be elevated in the serum following hindlimb inflammation, CNS induction of IL-1• may require an additional second messenger, such as IL-6.

In a behavioral model, using calibrated Von Frey filaments to test sensitivity to mechanical irritation, Samad et al show that in the setting of Cox-2 activation, rats were much more sensitive to painful stimuli. These hyperalgesic responses were blocked by intrathecal injection of the Cox-2 antagonist NS 398 or injection of YVAD, an inhibitor of IL-1• production. Intravenous injection did not produce these effects. Animals not subjected to hindpaw inflammation, who did not have upregulation of Cox-2, showed no effect from these inhibitors.

As Samad et al observe, the constitutional symptoms associated with inflammation and infection—such as fever, lethargy, malaise, and anorexia—are also related to increases in IL-1• and Cox-2. Inhibition of IL-1• production or administration of anti-inflammatory cytokines attenuate these effects.

COMMENTARY

As these data indicate, inhibiton of Cox-2 activity, either with selective drugs such as celecoxib or nonspecific NSAIDs, may significantly modify central pain pathways. But are these effects clinically significant? Since only a fraction of these drugs cross the blood brain barrier, it is unlikely that orally administered drug has a significant effect on these CNS processes. Cox-2 inhibitors should, thus, be designed to penetrate into the brain and spinal cord and, therefore, target central receptors. Other strategies might include downregulation of Cox gene expression by targeting IL-1• production or blocking IL-1• receptors. Because the current formulation of drugs such as celecoxib offers no particular benefit in this regard, agents such as ibuprofen, which are significantly less expensive and also affect Cox-2, should be considered first-line therapy in patients who tolerate them.

We should caution that these data should not be interpreted as evidence that Cox-2 plays a major role in pain that is neuropathic in nature (eg, postherpetic neuralgia or reflex sympathetic dystrophy) or in nociceptive pain that is purely mechanical without a significant inflammatory component (allodynia). As Samad et al's data clearly indicate, animals not subjected to the inflammatory injury did not show benefit from Cox inhibition and activation of C-fibers using electricity did not mimic CFA-associated Cox upregulation.

Thus, these data are not an indication that Cox-2 inhibitors have activity beyond that of an anti-inflammatory. Rather, they indicate that inflammation is very much a CNS process. The cascade of cytokine induction, Cox

activity, and prostaglandin production directly affects the spinal cord and brain. Because there may be important interactions between Cox and other mediators of central pain sensitization such as glutamate and substance P, it is likely that the ideal strategy for pain control will target multiple neurochemical substrates. **—alan z. segal**

Chronic Fatigue and Vasovagal Faints: Overlapping Syndromes?

ABSTRACT & COMMENTARY

Source: Kenny RA, et al. Chronic fatigue syndrome symptoms common in patients with vasovagal syncope. *Am J Med.* 2001;110:242-243.

Chronic fatigue syndrome (cfs) is characterized by unexplained disabling fatigue. Lightheadedness or syncope reportedly occur in 40-90% of CFS patients, which suggests an overlap of these 2 syndromes.[1]

Kenny and colleagues determined the prevalence of CFS symptoms[2] in consecutive patients with a primary diagnosis of vasovagal syncope confirmed by positive head-up tilt table testing. Patients with at least 2 syncopal episodes in the previous year without a cardiac cause for syncope and who did not have a diagnosis of CFS were studied. Study patients and age- and sex-matched controls completed a questionnaire for CFS symptoms.

Questionnaires completed by 62 syncope patients (63% women, mean age ± SD = 50 ± 21 years; range 16-83 years) were compared to questionnaires of 119 controls. The symptom criteria for CFS were fulfilled in 13 (21%) of patients but in only 1 control (*see Table*). Twelve of the 13 (92%) patients with CFS were women compared with 13 of the 49 (55%) patients without CFS.

Kenny et al recommend that CSF patients who have undiagnosed syncope should be investigated for vasovagal syncope and suggest that the 2 disorders may share a common mechanism.

COMMENTARY

Most people have fainted once or seen someone faint. The Framingham Study[3] recorded information on fainting. In the entire 26 years of surveillance of more than 5000 subjects, at least 1 syncopal episode was reported by 3% of the men and 3.5% of the women. More than 75% of the subjects had only a single faint. Isolated syncope in the absence of overt neurological and cardiovascular disease was not associated with increased morbidity or mortality and was not a frequent indicator of undiagnosed cerebrovascular disease.

Recurrent vasovagal syncope, in contrast, is a clinical problem that often is unresponsive to treatment, but symptoms may be improved by the use of selective serotonin reuptake inhibitors (SSRIs).Therefore, recurrent fainting resembles CFS. Like CFS, recurrent syncope also can be a disabling disorder, and quality of life deteriorates as a function of the recurrence of episodes. Syncopal episodes not only can produce physical trauma but also can create serious psychological discomfort. Employment, education, and social interactions may be severely restricted. SSRIs can improve clinical outcome in patients with refractory syncope (ie, those who are unresponsive to beta-blocking, vagolytic, negative inotropic, and mineralocorticoid therapy). Perhaps this is because SSRIs cause postsynaptic serotonin receptor to down regulate in the brainstem, thereby blunting the brain response to rapid shifts in cerebral serotonin levels.[5]

The causes of recurrent syncope are legion.[6] Clinicians should add CFS to the list. **—john j. caronna**

References

1. Bou-Holaigah I, et al. *JAMA.* 1995;274:961-967.
2. Fukuda K, et al. *Ann Intern Med.* 1994;121:953-959.
3. Savage DD, et al. *Stroke.* 1985;16:626-629.
4. DiGirolamo E, et al. *J Am Coll Cardiol.* 1999;33: 1227-1230.

Table

Symptoms of CFS in Syncope and Control Subjects

Symptoms	Patients		*P* value
	Syncope (n = 62)	Controls (n = 119)	
	n (%)	n (%)	
Fatigue > 6 months	18 (29)	2 (1)	< 0.001
Postexercise fatigue	15 (24)	7 (6)	< 0.001
Headache	19 (31)	26 (22)	< 0.001
Criteria for CFS	13 (21)	1 (1)	< 0.001
Arthralgia	25 (41)	25 (21)	< 0.006
Sleep disturbance	26 (42)	30 (25)	< 0.02
Myalgia	22 (35)	24 (20)	< 0.02
Impared cognition	6 (26)	19 (16)	< 0.1

5. Grubb BP, et al. *J Am Coll Cardiol.* 1994;24:490-494.
6. Ross TR. Syncope. In: Walton, ed. *Major Problems in Neurology*. London, England: WB Saunders; 1988.

Two New 'Alternative' Treatments for Tics

ABSTRACTS & COMMENTARY

Sources: Singer HS, et al. Baclofen treatment in Tourette syndrome. *Neurology.* 2001;56:599-604; Marras C, et al. Botulinum toxin for simple motor tics. *Neurology.* 2001;56:605-510.

Tourette syndrome (ts) and related tic disorders are relatively common chronic neuropsychiatric disorders that typically begin in childhood and may persist throughout adult life. Although epidemiological studies generally suggest an incidence of the order of 0.1-1%,[1] a more recent community-based study suggests that about 3% of school-aged children may have TS.[2] By either estimate, TS is by far the most common movement disorder of childhood.

The traditional treatment for the tics associated with TS include potent neuroleptics of the butyrophenone or phenothiazine class (so called "typical neuroleptics), which block D2 dopamine receptors. These agents, while highly effective at tic suppression, may have a problematic side effect profile in some patients. Atypical antipsychotic agents such as olanzapine (Zyprexa—Lilly) or risperidone (Risperdal—Janssen) may be preferred in some patients due to the potential of lesser risk of acute effects of D2 dopaminergic blockade, such as acute dystonia or parkinsonism. However, both typical and atypical agents may be associated with a risk of development of tardive movement disorders with long-term use. Alpha2- agonists, such as clonidine and guanfacine, may have some efficacy against tics but may be associated with significant sedation in many patients before adequate tic control is obtained. Thus, there is a need for new treatments for tics that do not have the problems that these agents may pose.

Singer and colleagues and Marras and colleagues have examined 2 such new treatments in the setting of small, but well-designed, clinical trials. Singer et al examined the use of baclofen, a GABA-B agonist, which a recent open-label trial[3] had suggested might be effective in suppressing motor tics. Nine children with TS completed a double-blinded, placebo-controlled crossover trial, with multiple outcome measures, including the Yale Global Tic Severity Scale (YGTSS). The YGTSS is composed of 2 subscores, a "total tic score (TTS)," which takes into account the number, frequency, intensity, and complexity of tics, and "tic interference score" (TIS), which assesses the effect of tics on issues such as self-esteem, school performance, job performance, and social functioning. Singer et al found that while baclofen treatment seemed to improve the YGTSS rating, this was largely due to an improvement in the TIS rather than the TTS. Simply put, baclofen did not reduce tics significantly but made them less bothersome to the patient.

Marras et al examined an entirely different approach. They examined botulinum toxin, which has been widely used in the treatment of focal movement disorders such as cervical dystonia and spastic dysphonia. Previous uncontrolled studies have suggested that botulinum toxin might be effective in the treatment of tics, particularly dystonic tics.[4,5] Marras et al examined 18 patients in a randomized, double-blinded clinical trial. In this study, there had to be a focus on a "target tic," which was the tic "sufficiently bothersome to the patient to require therapy." Using some of the same outcome measures as in the Singer et al study, Marras et al found that tic frequency and the "urge to tic" seemed to be reduced by botulinum toxin treatment, but the "interference" of these tics, using the TIS component or other measures, was not significantly affected. Simply put, botulinum toxin seems to reduce the tics significantly, but the residual tics are just as bothersome to the patient.

COMMENTARY

These papers highlight some of the difficulties one encounters in treating TS and related tic disorders, and they do so in a complementary fashion. The finding by Singer et al that baclofen may make the disorder less bothersome to the patient, without actually substantially reducing tics themselves, suggests that baclofen may act to reduce anxiety, self-awareness of tics, or perhaps some other behavioral factor. On the other hand, Marras et al find that botulinum toxin may reduce selected "target tics," but the residual tics are just as bothersome to the patient. The nature of TS is that it involves multiple motor tics that vary over time (ie, a varying "repertoire" of tics), so that it is understandable that reduction of a few selected tics out of many may not make that much of a difference to the patient. When a particular target tic is especially bothersome, botulinum toxin treatment may be especially useful; for example, it may be useful in the treatment of "malignant coprolalia," in which botulinum toxin injections into the vocal cord have been reported to be effective.[6]

One must also keep in mind that there is a strong association of a number of comorbid conditions with TS, including obsessive-compulsive disorder, anxiety

disorder, and attention deficit disorder. The sense of "interference" that a patient experiences from tics likely varies according to their overall neuropsychiatric profile. Thus, it is important to try to take a holistic approach in many patients, rather than just focus on the tics themselves.**—rosario trifiletti**

References

1. Apter A, et al. An epidemiologic study of Gilles de la Tourette's syndrome in Israel. *Arch Gen Psychiatry*. 1993;50(9):734-738.
2. Mason A, et al. The prevalence of Tourette syndrome in a mainstream school population. *Dev Med Child Neurol*. 1998;40(5):292-296.
3. Awaad Y. Tics in Tourette syndrome: New treatment options. *J Child Neurol*. 1999;14(5):316-319.
4. Jankovic J. Botulinum toxin in the treatment of dystonic tics. *Mov Disord*. 1994;9(3):347-349.
5. Kwak CH, et al. Botulinum toxin in the treatment of tics. *Arch Neurol*. 2000;57(8):1190-1193.
6. Scott BL, et al. Botulinum toxin injection into vocal cord in the treatment of malignant coprolalia associated with Tourette's syndrome. *Mov Disord*. 1996;11(4): 431-433.

Limb-Girdle Dystrophy Further Subcategorized

ABSTRACT & COMMENTARY

Source: Fanin M, et al. Calpain-3 and dysferlin protein screening in patients with limb-girdle dystrophy and myopathy. *Neurology*. 2001;56:660-665.

Among a database of approximately 5000 muscle biopsies performed for childhood or adult onset, proximal or distal, limb-girdle muscular weakness with elevated serum creatine kinase, 407 revealed a nonspecific myopathic or dystrophic process. All demonstrated normal dystrophin and sarcoglycan by Western blot or gene analysis, and normal telethonin and merosin by immunoflourescence. Using Western blot and immunohistochemistry, these 407 biopsies were tested for calpain-3 and dysferlin deficiency. Fifty-eight biopsies from clearly defined neuromuscular diseases, including Duchenne, Becker, and facioscapulohumeral muscular dystrophy, inflammatory myopathy, metabolic, and congenital myopathy, served as controls.

Strikingly, calpain-3 deficiency was found in 16% (n = 66), with total absence in 47% (n = 31) and severe deficiency (3-50% of control) in the remainder. Dysferlin deficiency was seen in 6.5% (n = 26), being absent in 35% (n = 9), and severely deficient (20% or less of control) in 65% (n = 17). Among patients with a limb-girdle muscular dystrophy (LGMD) phenotype, 28% (53/191) had calpain-3 deficiency, and among those with distal myopathy, 60% (21/35) were dysferlin deficient. Immunoblot analysis is useful in the diagnosis of unclassified myopathy or dystrophy, where approximately 25% will be calpain-3 or dysferlin deficient.

COMMENTARY

LGMDs have long resisted orderly classification. Recently, positional cloning techniques have demonstrated 11 types of genetically defined LGMDs.[1] Three autosomal dominant LGMDs are designated 1A, 1B, and 1C—the last being the caveolin 3 gene (*see Table*). Autosomal recessive forms include deficiency of calpain, dysferlin, or sarcoglycan. Sarcoglycanopathies are divided into 4 types based on alpha, beta, gamma, or delta sarcoglycan deficiency (*see Table*). Epsilon sarcoglycan has also been identified, localizing to chromosome 7q21, but is not yet known to be involved in muscle disease. Calpain-3 and dysferlin deficiency (*see Table*) appear to be

Table

LGMD's Specific Chromosomal Identities

	Chromosome	Inheritance (Autosomal)
LGMD 1A	5q22-24	Dominant
LGMD 1B	1q11-21	Dominant
LGMD 1C	3p25	Dominant
Sarcoglycanopathy alpha	17q12-21.33	Recessive
Sarcoglycanopathy beta	4q12	Recessive
Sarcoglycanopathy gamma	13q13	Recessive
Sarcoglycanopathy delta	5q33-34	Recessive
Calpain-3 deficiency	15q15.1-21.2	Recessive
Dysferlin deficiency	2p13	Recessive

the most common forms of LGMD. Two other mutations, at chromosomes 17q11-12 and 9q31-33, also result in autosomal recessive LGMD, but their gene products remain undefined.

Calpain-3 (also called p94) is a skeletal-muscle-specific, calcium-dependent, cysteine protease that interacts with titin (connectin) and exists in the cytosol and nucleus. Its function is unclear, perhaps regulating muscle cell differentiation, but its pathogenic role in LGMD remains puzzling. Dysferlin localizes to the muscle membrane and has been implicated both in LGMD2B and Miyoshi myopathy, a distal form of muscular dystrophy, but again its role is undefined. Further clinical heterogeneity of dysferlin deficiency has recently been reported in a family with anterior compartment distal leg weakness rapidly progressing to severe proximal weakness. Muscle biopsy demonstrated absent dysferlin immunostaining, and nucleotide sequence analysis revealed a single base pair deletion creating a frameshift mutation of the dysferlin gene.[2] **—michael rubin**

References

1. Bushby KM, et al. *Brain*. 1999;122:1403-1420.
2. Illa I, et al. *Ann Neurol*. 2001;49:130-134.

Brief Alert

Modafinil for Myotonic Dystrophy

Source: Damian MS, et al. Modafinil for excessive daytime sleepiness in myotonic dystrophy. *Neurology*. 2001;56: 794-796.

Hypersomnia is a prominent feature of myotonic dystrophy (MyD), although, interestingly, it is more often remarked upon by relatives than by patients. Not felt to be true narcolepsy, its cause remains obscure. Modafinil, useful in narcolepsy, may nevertheless be efficacious for excessive daytime sleepiness (EDS) in MyD. In an open label trial, Damian and colleagues describe 8 patients with genetically proven MyD (expanded CTG repeat on chromosome 19q13.13) and 1 with maternally inherited proximal myotonic myopathy (PROMM). Each patient received 200-400 mg/d modafinil for a minimum of 16 weeks. All felt disabled by their EDS prior to the modafinil. With treatment, mean sleep latency (measured by MSLT) significantly increased, mean Epworth Sleepiness Scale score decreased, and all patients felt subjectively better. Modafinil was well tolerated, without significant side effects, blood pressure remained normal, and nighttime sleep was unimpaired. Clearly, it is time to proceed with a placebo-controlled, double-blind, multicenter trial.

COMMENTARY

With this effective response and the relatively small number of persons who used it, it seems to Damian et al that its duration of effect should first be tested by the enlarging pioneer patients and providing a 6-month test time table. **—michael rubin**

CME Questions

22. Persons in a state of mild cognitive impairment have a Clinical Dementia Rating Scale score of what?

a. 0
b. 0.5
c. 1
d. None of the above

23. All the following are significantly more prevalent in patients with recurrent vasovagal syncope than in controls *except*:

a. chronic fatigue.
b. fatigue post exercise.
c. headaches.
d. impaired cognition.
e. arthralgias

24. Regarding the treatment of Tourette syndrome, which of the following is true?

a. Baclofen seems to reduce tics in a controlled study.
b. Botulinum toxin seems to reduce target tics and reduce discomfort in a controlled study.
c. Baclofen may produce the sense of less interference of residual tics on self-esteem, school, and job performance.
d. Botulinum toxin may produce the sense of less interference of residual tics on self-esteem, school, and job performance.

25. Limb-girdle muscular dystrophies is/are most often due to deficiency of what?

a. calpain and dysferlin
b. dysferlin and sarcoglycan
c. sarcoglycan and calpain
d. None of the above

In Future Issues:

CADASIL and Genetic Roots