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## Position Paper: Rethinking Thymectomy

ABSTRACTS & COMMENTARY

**Sources:** Gronseth GS, Barohn RJ. Practice parameter: Thymectomy or autoimmune myasthenia gravis. Report of the quality standards subcommittee of the American Academy of Neurology. *Neurology* 2000;55: 7-15; Kissel JT, et al. Treatment of myasthenia gravis: A call to arms. *Neurology* 2000;55:3-4.

Thymectomy is "...advisable in practically all patients with uncomplicated myasthenia gravis (MG)" (Adams RD, Victor M, Ropper AH. *Principles of Neurology*. 6th ed. New York, NY: McGraw Hill; 1997:1469). Practice parameter guidelines from the Quality Standards Subcommittee of the American Academy of Neurology now give pause to this suggestion. Searching the National Library of Medicine's Medline database from 1966 to 1998, 310 articles discussing MG and thymectomy were identified. Review of these, including references, garnered 28 controlled, non-blinded, studies discussing 21 MG cohorts (due to overlap of patient groups) treated with and without thymectomy. Thymectomy was not randomly assigned, and surgical technique (trans-sternal vs trans-cervical) was in many cases not specified. Follow-up varied from three to 28 years, and the number of patients lost to follow-up was usually omitted.

Thymectomy and improvement were significantly associated in only seven of 15 studies reporting medication-free remission, eight of 12 studies reporting patients on or off medication, eight of 13 reporting improvement, and four of 13 reporting survival. Most studies showed no significant benefit. Thymectomized patients were twice as likely to achieve medication-free remission, 1.7 times as likely to improve, and 1.6 times as likely to become asymptomatic. They also tended to be younger and female (usually associated with better outcomes), yet generalized and severe (usually associated with poorer outcomes). Controlling for these variables resulted in conflicting findings. Thymectomy for non-thymomatous MG is a therapeutic option but its benefit has not been conclusively established.

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## INSIDE

## COMMENTARY

Controlled trials will be needed to determine the true efficacy of thymectomy in MG. Alternative forms of immunosuppressive therapy are also necessary, aimed at both the B-cell (antibody forming) and T-cell (final common pathway) arms of the autoimmune response to nicotonic Ach receptors in MG. Developing tolerance to the precise MG antigen, presently unknown, or inducing production of inactive, rather than active, autoantibodies are alternative approaches that must be examined. Vaccination, by oral, nasal, or systemic route using an inciting antigen is an approach presently being investigated in multiple sclerosis (Weiner HL. *Ann Rev Med* 1997;48:341-351), with suppression of lymphokine-releasing T cells the purported mechanism. Torpedo AchR has been the antigen used experimentally in allergic MG (Okumura S, et al. *Ann Neurol* 1994;36:704-713), although human AchR receptor subunits may be effective as well (Lindstrom JM. *Muscle Nerve* 2000;23:453-477). Toxins conjugated to AchR, with the intent to kill B cells, have not been successful. Using monovalent Fab fragments of the immunoglobulin to bind autoantibody would prevent complement fixation as these fragments lack the Fc region of the immunoglobulin. Crosslinking of ACh receptors would also be constrained in the absence of the bivalent F(ab)2 fragment. However, Fab is too rapidly cleared from the bloodstream for this approach to be effective. Further study is necessary to pursue the best treatment for MG. **—michael rubin**

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# The Serotonin and Migraine Story Continues

ABSTRACT & COMMENTARY

**Source:** Leone M, et al. The serotonergic agent m-chlrophenylpiperazine induces migraine attacks: A controlled study. *Neurology* 2000;55:136-139.

By now it seems clear that serotonin or 5-hydroxytryptophan (5-HT) is important in the pathophysiology of migraine. The exact mechanism, however, has not been fully elucidated. In an attempt to better understand at least the pertinent receptors involved, Leone and colleagues looked at the incidence of migraine in subjects given m-chlorophenylpiperazine (mCPP), a serotonin agonist with specificity at the 5-HT2B,2C,1A receptors. Thirty-nine patients (20 controls and 19 migraineurs with aura) were enrolled in a double-blind study to receive either 0.5 mg/kg of oral m-CPP or oral placebo.

Incidence of headache was reported for the following 24 hours. Serum levels were measured in both groups and found to be comparable. The total number of headaches after m-CPP (n = 18; 46.2%) did not differ from the total number after placebo (n = 12; 30.8%). There were, however, more IHS defined migraines after m-CPP (n = 16; 41% vs n = 5; 13%) ($P < 0.02$) than in the placebo group. Leone et al conclude that m-CPP can provoke more migraines than placebo and indicate that migraineurs are more likely to develop headache on m-CPP challenge than control subjects. The findings support the role of 5-HT2B,2C,1A receptors in the pathophysiology of migraine. Leone et al do not comment on why the overall incidence of headache was comparable in each group.

## COMMENTARY

The relationship of serotonin and migraine has been well known. Over the years, several observations have been noteworthy: serum 5-HT levels increase during migraine; platelets release 5-HT during migraine; 5-HT metabolites appear in the urine of patients after a migraine headache; and serotonin infusions will provoke

migraine. Furthermore, the recognition that 5-HT 1D/1B receptors are widely expressed on cerebral vasculature led to the development of the triptan class of migraine-abortive drugs. 5-HT is widely expressed within the brainstem and cortex, regions in which other important receptor types have been implicated. This study demonstrates a significant role for 5-HT2B,2C,1A receptor subtypes, which may open doors for better understanding of the central mechanism and point the way to future medication interventions. **—jeffrey reich**

## Treatment for Migraine Aura?

ABSTRACT & COMMENTARY

**Source:** Kaube H, et al. Aura in some patients with familial hemiplegic migraine can be stopped by intranasal ketamine. *Neurology* 2000;55:139-141.

Migraine aura is characterized by transient reversible neurologic symptoms. Recent dynamic blood flow studies have correlated such clinical symptoms with slowly spreading perfusion changes across the cortex. The pattern resembles the cortical spreading depression (CSD) phenomenon observed in experimental animals. In such models, CSD is mediated by both the diffusion of extracellular potassium and excitatory amino acids. In fact, CSD can be blocked in animals by glutamate NMDA receptor antagonists. Kaube and colleagues attempted the first known clinical study using the NMDA antagonist ketamine to halt aura symptoms in patients diagnosed with familial hemiplegic migraine (FHM).

The study was unblinded given the severity of the aura symptoms and the potential psychotropic side effects of ketamine. Patients were instructed to self-administer 25 mg of intranasal ketamine at the first onset of aura. The response was measured by self-assessment questionnaires completed every 15 minutes and extensive follow-up interviews. Eleven patients from seven families with diagnosed FHM were enrolled and 25 migraine aura attacks were treated. Genetic linkage analysis to FHM locus CACNA1A on chromosome 19p13.1 was performed on all seven families. Five patients from three families reported improvement after ketamine for all 14 attacks. Improvement was defined as reduction in duration and severity of neurologic symptoms as none spread from one symptom to another. Six patients had no benefit after 11 treated attacks. Kaube et al make special note that only two patients reported a reduction in headache severity after ketamine. Furthermore, they noted that the response was not related to the presence or absence of a proven linkage to the chromosome 19p13 locus. Kaube et al conclude that migraine aura can be selectively attenuated by the NMDA antagonist ketamine. This provides further evidence that migraine aura is caused by CSD and that NMDA antagonists might be useful in the management of severe migraine.

### COMMENTARY

Several points are worth noting. The methodological compromises of this study greatly limit the degree to which conclusions can be drawn. Migraine is too complicated and its symptoms are too subjective to rely on unblinded subjects and observers as well as nonplacebo controlled trials. Furthermore, a rating scale might help actually to quantitate the severity of aura symptoms and the subsequent response to ketamine. Future studies correlated with functional imaging would be equally important. But these are not criticisms as much as questions that are provoked by such an intriguing study. It raises not only the issue of CSD and aura but suggests possible treatment options to explore. The observation that blocking the aura did not necessarily prevent headache is important. In the current trigeminal vascular model of migraine, neurogenic inflammation is presumed to be induced around cranial vasculature by CSD. In other words, migraine aura and migraine headache are serial processes. However, it may be that both aura and headache follow in parallel from a central process. Indeed, Diener and colleagues (*Nat Med* 1995;1:658-660) have suggested a brainstem location for such a "migraine generator" based upon PET studies of spontaneous migraine attacks. **—jeffrey reich**

## More Evidence That rtPA Therapy Has a Sustained Benefit

ABSTRACT & COMMENTARY

**Source:** Schmullin S, et al. One-year follow up in acute stroke patients treated with rtPA in clinical routine. *Stroke* 2000;31:1552-1554.

A recent report of long-term follow-up of the NINDS rtPA patients (The NINDS rtPA Stroke Study Group. *N Engl J Med* 1995;333:1581-1587) indicated that benefit was sustained at one year (Kwiatkowski TG, et al. *N Engl J Med* 1999;340:1781-1787) compared

with the placebo group. Patients treated with rtPA within three hours after the onset of acute stroke symptoms were at least 32% more likely to have minimal or no disability at one-year follow-up. In the present study from Cologne, Schmulling and associates report the results of a 12-month follow-up of 150 consecutive patients with acute ischemic stroke treated with rtPA following a protocol comparable to the American Heart Association guidelines (Grond M, et al. *Stroke* 1998;29: 1544-1549; Adams HP, et al. *Circulation* 1996;94:1167-1174).

Baseline characteristics of the Cologne patients were comparable to those of the NINDS study except for a somewhat younger age (mean, 63 years vs 69 years in NINDS) and a less severe neurological deficit (median NIH stroke scale [Lyden P, et al. *Stroke* 1994;25:2220-2226] 11 vs 14 in NINDS).

Altogether, 132 patients had supratentorial and 18 had subtentioral stroke. Clinical outcome was assessed by physical examination and scored using the NIH Stroke Scale, the Rankin Scale (Van Swieten JC, et al. *Stroke* 1998;19:604-607), and the Barthel Index (Mahoney FI, Barthel DW. *Md Med J* 1965;14;61-65) at three months and 12 months by a structured telephone interview with the patient and/or caregivers.

Sixteen patients died during the first three months of observation. Parenchymal hemorrhage occurred in 12 patients (8%). In six patients, the cerebral hemorrhage was symptomatic (4%) and in two of these fatal. Eight others died of primary stroke-related causes and six others died of concomitant disease, especially cardiac.

At one year, 41% of patients showed minimal or no disability (Rankin, 0-1), 24% were moderately disabled (Rankin, 2-3), and 20% were severely disabled (Rankin, 4-5). Fifty-one percent were functionally independent (Barthel Index, 50-100). Functional outcomes of the Cologne group were comparable to those of the NINDS rt-PA Stroke Trial treated patients (*see Table*).

**Table**

**Barthel Index of Functional Outcome at 12 months in Cologne Study and NINDS rtPA Stroke Trial Patients**

| Barthel Index* | (95-100) | (55-90) | (0-50) | Death |
|---|---|---|---|---|
| Cologne Study | 51% | 21% | 13% | 15% |
| NINDS rt-PA treated patients | 50% | 13% | 13% | 24% |
| NINDS placebo patients | 38% | 16% | 17% | 28% |

*Barthel Index: good, 95-100; moderate, 55-90; and poor functional outcome, 0-50

**COMMENTARY**

Even though the efficacy of the rtPA treatment for acute ischemic stroke has been demonstrated in several controlled trials, many neurologists remain reluctant to use it in clinical practice. The concern is that in routine use, thrombolytic treatment may have a higher complication rate and a lower effectiveness than when it is administered under ideal study conditions. The evidence from this study is that a sustained benefit at one year can be obtained from rtPA treatment in acute stroke patients under routine clinical conditions. If the guidelines for treatment and management are followed closely, the risks and benefits of thrombolytic treatment in everyday practice are similar to those obtained under the conditions of controlled trials. It is hoped that these observations will encourage the increased use of rtPA in appropriate clinical circumstances. **—john j. caronna**

# Can TCD Monitoring During Carotid Endarterectomy Reduce the Risk of Perioperative Stroke?

ABSTRACT & COMMENTARY

**Source:** Ackerstaff RG, et al. Association of intraoperative transcranial Doppler monitoring variables with stroke from carotid endarterectomy. *Stroke* 2000;31:1817-1823.

Stroke is the most common major complication of carotid endarterectomy (CEA). Among experienced surgeons, acceptable stroke rates as documented by large multicenter trials (e.g., NASCET) range from 5-6%. Both embolism and/or hemodynamic compromise may account for these strokes.

Transcranial Doppler (TCD) monitoring of the middle cerebral artery (MCA) during CEA may provide useful information about both microembolic signals to the brain and significant flow limitations during carotid cross clamping. Ackerstaff and colleagues report on 1058 patients undergoing CEA in two centers in the Netherlands and the United States. There were 39 strokes (31 ischemic, 8 hemorrhagic). Diagnosis of stroke was made retrospectively based on chart review. TCD characteristics associated with a poor outcome were: emboli detected during the dissection, during surgical wound closure, accompanying a drop of 90% or more in MCA flow velocity at cross-clamping, and an

increase of 100% or more in pulsatility index at clamp release. Emboli detected during shunting and during clamp release were not significant. These latter emboli are predominantly gaseous rather than particulate and are not typically associated with the development of neurological deficits.

Ackerstaff et al found a larger number of post-op strokes among patients with pre-existing cerebral ischemia. Stroke risk in symptomatic patients undergoing CEA has been previously shown to be double that of asymptomatic individuals (6% in NASCET vs 3% in ACAS). Ackerstaff et al's data also indicate that stenoses of 70% or more were inversely related to outcome. They suggest that cross clamping of severely stenosed arteries had less of an influence on cerebral blood flow that did cross clamping of arteries with lesser stenoses.

**COMMENTARY**

Because the benefit of CEA is so greatly dependent on low surgical morbidity and mortality, development of methods to make this procedure safe are of utmost importance. The reactions to changes in neuroprotective monitoring during CEA depend almost entirely upon the operating surgeon. Ipsilateral hemispheric slowing on EEG may indicate inadequate collateral circulation and a need for shunting during carotid cross clamping. Other surgeons depend on measurement of carotid stump pressures. As shown by Ackerstaff et al, a drop in MCA flow velocities is another useful indicator of a need for shunting.

Because embolism rather than hemodynamic change may explain the cause of a majority of CEA-associated strokes, maintenance of blood flow alone will not assure a safe procedure. As Ackerstaff et al showed, microembolic signals detected by TCD significantly relate to adverse outcomes. Upon hearing such signals in the operating room, the surgeon might modify his technique of carotid dissection or more quickly proceed to distal clamping of the carotid artery. As observed in the accompanying editorial (*Stroke* 2000;31:1799-1801), Ackerstaff et al's study would be strengthened by better quantification of primary methods. Specific criteria should be provided to surgeons to differentiate between occasional benign signals and showers of potentially dangerous emboli. TCD monitoring could also be extended to the immediate 24 hours following surgery, a time when further emboli may occur. Such emboli might be prevented by anticoagulation with heparinoids or antiplatelet agents.

Most experts know that the majority of microembolic signals detected by TCD are asymptomatic. For instance, continuous monitoring by TCD during aortic manipulation in cardiac surgery has not consistently correlated with neurological outcome. (Barbut D, et al. *Ann Thorac Surg* 1997;63:1262-1267). Immediately following Ackerstaff et al's report is another by Barth and colleagues (*Stroke* 2000;31:1824-1828) who report on 53 patients studied with diffusion-weighted imaging (DWI) before and after CEA. Two patients suffered small infarcts on DWI. Both were asymptomatic. Microemboli detected by TCD as well as plaque ulceration and a need for shunting were not shown to correlate with the rare occurrence of stroke as measured by DWI. These observations should be taken with caution, however, as they are based entirely on two patients who had positive DWI outcomes.

Finally, Ackerstaff et al present an intriguing finding that marked increases in flow on clamp release may be a marker for the postoperative hyperperfusion syndrome. It is not clear from the data whether any of the adverse post-procedure events occurred by this mechanism. **—alan z. segal**

# Diabetic Amyotrophy is Immune-Mediated

ABSTRACT & COMMENTARY

**Source:** Klekar P, et al. Distinctive pathologic findings in proximal diabetic neuropathy (diabetic amyotrophy). *Neurology* 2000;5:83-88.

Fifteen patients, eight men and seven women, ages 49-79 years, with proximal diabetic neuropathy (PDN, diabetic amyotrophy) of 5-52 weeks duration, underwent nerve and muscle biopsy. PDN was characterized by progressive, proximal, painful, asymmetric weakness. Diagnosis required the absence of complicating illness, including peripheral vascular disease, structural spinal cord or pelvic disease, previous radiation, or malignant infiltration of lumbar plexus. None had evidence of polyneuropathy and all demonstrated active denervation on electrodiagnostic studies. Two diabetic patients without PDN and five nondiabetics, two each with chronic inflammatory demyelinating polyneuropathy and muscular dystrophy, and one with inclusion body myositis, served as biopsy controls.

Four PDN patients, biopsied within six weeks (n = 3) or during flare-ups of symptoms (n = 1), demonstrated transmural polymorphonuclear infiltration of epineurial postcapillary venules, without fibrinoid necrosis or thrombosis. Biopsies in the other patients, performed at 3-12 months after onset, were absent of these features. Six patients, however, showed T lymphocyte perivascular mononuclear collections, without vasculitis but involving small epineurial vessels. Neurogenic atrophy was seen in all muscle biopsies with endomysial lymphocytic infiltration in only one patient. No inflammation or mural infiltration was observed in any of the controls. PDN is an immune-mediated vasculitis, and not an ischemic microangiopathic neuropathy. The inciting antigen remains unknown.

### COMMENTARY

Using indirect immunofluorescence, circulating autoantibodies have been well reported in diabetic patients. Among 154 diabetic patients, 12% demonstrated anti-GM1 antibody, predominantly in those with distal symmetric polyneuropathy with demyelinating features (*Contemp Intern Med* 1994;16:41-55). Antiphospholipid antibodies, with their tendency to thrombotic complications and neural insults, were seen in 88% (n = 18) of this group compared to 2% of the general population and 32% of diabetics without neurologic complications (*Diabetes Care* 1995;18:1225-1232). In another report, antiglutamic acid decarboxylase (GAD) autoantibodies were present in 55% and 21% of type I and type 2 diabetics, respectively, supporting an autoimmune role in diabetes pathogenesis (*Diabetes Res Clin Pract* 2000;49:33-40). Circulating antiendothelial (antipericyte) autoantibodies may be active in diabetic retinopathy (*Retina* 1999;19:390-400). Anti-autonomic nervous system antibodies, including autoantibodies to adrenal medulla, vagus nerve, and sympathetic ganglion cells, are only rarely observed in symptomatic diabetic autonomic neuropathy (*Diab Med* 1997;14:461-465). Greater insulin requirement in the early years of clinical diabetes appears to correlate with multiple autoantibody positivity (anti GAD, anti IA-2 protein, anti-insulin, anti-islet cell) and may reflect more aggressive islet-cell destruction (*J Clin Endocrinol Metab* 1999;84:1534-1539). Prevention of autoimmune diabetes and its complications may involve protecting susceptible cells (islet cells, venules) from autoimmune attack by promoting immune tolerance in the host (*Drugs* 1997;53:943-956). **—michael rubin**

# Reflex Sympathetic Dystrophy

ABSTRACT & COMMENTARY

**Source:** Goldstein DS, et al. Sympathetic innervation and function in reflex sympathetic dystrophy. *Ann Neurol* 2000; 48:49-59.

Sympathetic neurocirculatory function was examined by positron emission tomography ([PET] in 9 men and 21 women), aged 25-55 years, with reflex sympathetic dystrophy (RSD). 13N-ammonia (a perfusion imaging agent) and 6-[18F]flourodopamine (a sympathoneural imaging agent) were used to assess local perfusion and sympathetic innervation. The rate of norepinephrine spillover that escaped into the venous system from neuronal reuptake was estimated during intravenous infusion of 3H-norepinephrine. Local norepinephrine turnover was examined by regionally measuring its main metabolite, dihydroxyphenylglycol; local norepinephrine synthesis was examined by regionally measuring L-dihydroxyphenylalanine. Both were measured before and after ganglionic blockade using intravenous trimethaphan, to determine whether RSD pain is maintained by sympathetic nerve traffic.

RSD was diagnosed on the basis of persistent, post-traumatic pain that spread beyond the distribution of any single nerve (complex regional pain syndrome, type I) associated with hair loss, dystrophic skin or nail changes, altered sweating or skin color or temperature, swelling, allodynia, and disuse muscle atrophy. Patients continued taking pain medication during the study but adrenoreceptor-active drugs and tricyclic antidepressants were discontinued. Comparison was made to the contralateral limb, age-matched normal controls, and previously reported normal data. Statistical analysis used dependent-means T tests and repeated measures ANOVAs.

PET scanning using 13N-ammonia radioactivity was decreased, and perfusion adjusted 6-[18F]flourodopamine was increased on the affected side. This indicated decreased perfusion in the affected limb in the presence of a normal amount of sympathetic terminal innervation. No differences were appreciated between affected and unaffected limbs in norepinephrine spillover, dihydroxyphenylglycol, or L-dihydroxyphenylalanine plasma levels. Trimethaphan decreased pain in only two of 12 previously sympathectomized patients, indicating a pain mechanism independent of postganglionic nerve traffic. In RSD, sympathetic inner-

vation and norepinephrine synthesis is symmetrical, sympathetic terminal innervation remains intact, and perfusion is decreased. This indicates that pain is generally independent of sympathetic outflow in most cases of RSD. Complex regional pain syndrome is, thus, the preferred term for this baffling disorder.

**COMMENTARY**

Sympathectomy may be beneficial in RSD, not due to the significance of the sympathetic nervous system in maintaining the pain, but rather due to placebo effect or deafferentation of primary visceral fibers that run with sympathetic nerves (*BMJ* 1998;316:792-793). Infusion of phenylephrine, an alpha-1 adrenergic agonist that should exacerbate sympathetically maintained pain, did not do so in 29 patients with causalgia, RSD, or polyneuropathy (*Neurology* 1994;44:1010-1014). Indeed, saline sympathetic blocks produced an average of 20 hours of relief in RSD (*Clin J Pain* 1998;14:216-226) and meta analysis of sympathectomy in RSD found it lacking (*Pain* 1997;73:123-139). Support for sympathetic involvement in RSD is shown by thermal hyperalgesia being enhanced by adrenergic agonists in capsaicin-treated skin (*J Auton Nerv Syst* 1998;69:96-102), and dampened by phentolamine (*Pain* 1997;69:79-85). These data, however, are refuted by elegant studies showing that natural stimulation of sympathetic efferents, by heating and cooling in a thermal suit, did not affect pain or hyperalgesia in capsaicin-treated areas. Has the sympathetic hypothesis been put to rest? Not yet, but it does appear to be fading. Meanwhile, whether the diagnosis is called causalgia, traumatic angiospasm, acute trophoneurosis, or postinfarctional sclerodactyly, we believe that for the present, the terms complex regional pain syndrome type I (pain spreading beyond the site of injury), or type II (causalgia caused by a peripheral nerve injury) remain as appropriate labels. **—michael rubin**

## Creatine for McArdle Disease

ABSTRACT & COMMENTARY

**Source:** Vorgerd M, et al. Creatine therapy in myophosphorylase deficiency. *Arch Neurol* 2000;57:956-963.

Creatine therapy benefits in mitochondrial cytopathies (*Muscle Nerve* 1997;20:1502-1509), as well as various forms of muscular dystrophy (MD), including facioscapulohumeral, Becker, Duchenne (n = 8), and sarcoglycan-deficient MD (*Neurology* 2000; 54:1848-1850). It also improves exercise performance in myophosphorylase deficiency (McArdle disease). Nine McArdle patients, including six women and three men (mean age, 39.1 years) entered into a double-blind, placebo-controlled, crossover study using placebo or creatine, 150 mg/kg/d, for one week followed by 60 mg/kg/d for four weeks. A four-week washout period separated the active and placebo phases. Measurements included maximal ergometric bicycle-exercise workload and duration, fatigue severity scale (*Arch Neurol* 1989;46:1121-1123), grading of exercise-induced muscle pain, and frequency of muscle pain per week. Phosphorous 31 NMR spectroscopy of the right calf (*Neuromusc Disord* 1998;8:480-488), and surface electromyographic (sEMG) spectral distribution were obtained (*Ergonomics* 1996;39:298-313). Statistical analysis was performed with two sample *t* tests and the sign test.

All nine patients completed the study. FSS and maximal ergometric bicycle-exercise workload and duration did not differ between the two study arms. Four persons, however, reported reduced frequency, and five reported subjective improvement of muscle pain and wished to continue creatine treatment. Creatine resulted in a significantly increased force-time integral on $^{31}$P-NMR data during ischemic, but not aerobic, exercise, and increased EMG amplitude was recorded during sustained contraction. Other than transient mild headache and dizziness in a single patient, no adverse effects were reported. Creatine is safe and often beneficial for McArdle disease. **—michael rubin**

## Botulinum Injected into the Salivary Glands Relieves Excessive Saliva in ALS

ABSTRACT & COMMENTARY

**Source:** Geiss R, et al. Injections of botulinum toxin A into the salivary glands improve sialorrhoea in amyotrophic lateral sclerosis. *J Neurol Neurosurg Psychiatry* 2000;69: 121-123.

Patients suffering the late stages of bulbar amyotrophic lateral sclerosis (ALS) frequently develop chronic, excessive sialorrhoea. Similar problems also may distress patients with pseudobulbar palsy due to cerebral vascular disease or, occasionally, multiple sclerosis. Geiss and associates treated five patients

with bulbar ALS and disabling sialorrhoea. They used Botulinum toxin A, which prevents acetylcholinesterase release at appropriate motor and autonomic nerve terminals. The drug has found worth in treating other autonomic disorders but in this case the target consisted of the salivary glands. Both parotid glands were injected and reinjected two weeks later if the initial response was not sufficient. The submandibular glands were only injected if the parotid injections had been unsuccessful. Effect was quantified by checking the patients' reduction of paper towels following treatment as well as grossly evaluating their own response between none, moderate, or markedly successful. Salivary secretion was measured by technetium-99m pertechnetate before the first Botox dose and two weeks after the injection started. Sialorrhea declined within 3-5 days after the first administration. Three patients showed a "marked improvement" after treatment and reported a higher quality of life. Another had moderate improvement and the fifth reported no help. This last individual apparently had a rapid downhill course of his total disease.

Geiss et al report several parallel findings. One was that the salivary secretion of all of the subjected ALS patients was less than half of the normal flow. (Possibly, this reflected a loss of salivary stimulation because of their limited oral food stimulus).

### COMMENTARY

This is a useful report because it shows a possibility of reducing excess salivation in patients with oral cancers, traumatic facial injury, cranial polyneuropathy, and, perhaps other disturbances. How long the benefit will last is as yet hard to tell. **—fred plum**

## CME Questions

**12. Diabetics demonstrate:**

a. antiglutamic acid decarboxylase (GAD) autoantibodies are in 10% and 21% of type I and type 2 diabetics, respectively.
b. multiple autoantibody positivity including anti GAD, anti IA-2 protein, anti-insulin, and anti-islet cell autoantibodies.
c. anti-GM1 antibodies, predominantly in those with proximal asymmetric neuropathy.
d. antiphospholipid antibodies, in up to 28%.
e. None of the above

**13. Reflex sympathetic dystrophy:**

a. is due to capsaicin induced hyperalgesia.
b. is due to hyperactivity of phenylephrine, an alpha-1 adrenergic agonist.
c. is due to deafferentation of primary visceral fibers with resultant sympathetic fiber disinhibition.
d. may have nothing to do with the sympathetic nervous system.

**14. All of the following statements regarding carotid endarterectomy (CEA) are true *except*:**

a. Stroke may occur on a hemodynamic or embolic basis.
b. Microemboli detected by transcranial doppler (TCD) may be gaseous or particulate.
c. Emboli detected by TCD during shunting are more dangerous than those during initial dissection or wound closure.
d. Other methods such as EEG may be useful means of neurological monitoring during CEA.

**15. Regarding myasthenia gravis (MG):**

a. thymectomy is indicated in most cases of nonthymomatous MG.
b. controlled studies should be undertaken to determine the true place of thymectomy in the treatment of MG.
c. human AchR receptor subunits may be used as a vaccination to treat MG.
d. the use of monovalent Fab fragments, administered IV to bind pathologic autoantibody as a treatment for MG will soon be FDA approved.
e. T cells play no significant role in the pathogenesis of MG.

**16. A dose of 25 mg of intranasal ketamine in familial hemiplegic migraine patients was shown to:**

a. provoke an actual migraine aura and headache.
b. inhibit the duration and severity of migraine aura.
c. inhibit the intensity and severity of migraine headache.
d. inhibit the "brainstem generator" associated with migraine.

**17. At 12 months after treatment with rtPA, the percentage of patients who can be expected to have minimal or no disability (Barthel) is approximately:**

a. 50%.
b. 40%.
c. 30%.
d. 25%.
e. 15%.

## Correction

The article, "Diffusion-Weighted Imaging II: Is There a New Gold Standard in Acute Stroke Imaging?" in the August 2000 issue of *Neurology Alert* contained an error. MCA should have been middle cerebral artery throughout the article. We regret any confusion this may have caused. ❖

## In Future Issues:

Central Spinal Fluid Sulfatide