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INSIDE

Conflicting Data on Benefit of IVIG Treatment in MS

ABSTRACTS & COMMENTARY

Synopsis: *Intravenous immunoglobulin treatment for the first year from onset of the first neurological event suggestive of demyelinative disease significantly lowers the incidence of a second attack and reduces disease activity as measured by brain magnetic resonance imaging.*

Sources: Achiron A, et al. Intravenous Immunoglobulin Treatment Following the First Demyelinating Event Suggestive of Multiple Sclerosis. *Arch Neurol.* 2004;61:1515-1520; Sorensen P, et al. IV Immunoglobulins As Add-on Treatment to Methylprednisolone For Acute Relapses in MS. *Neurology.* 2004;63:2028-2033; Hommes O, et al. Intravenous Immunoglobulin in Secondary Progressive Multiple Sclerosis; Randomised Placebo-Controlled Trial. *Lancet.* 2004;364:1149-1156.

ACHIRON AND COLLEAGUES CONDUCTED A RANDOMIZED, PLACEBO-controlled, double-blind study of IVIG within 6 weeks of a first demyelinating event suggestive of multiple sclerosis. Patients received IVIG treatment (2 g/kg loading dose) or placebo and then boosters (0.4 g/kg) every 6 weeks for 1 year. Neurological and clinical assessments were done every 3 months, and a brain MRI was done at the baseline and the end of the study.

The cumulative probability of developing clinically definite MS, ie, a second neurologic event, was lower in the IVIG group vs the placebo group (rate ratio, 0.36 [95% confidence interval 0.15-0.88]; $P = 0.03$). Patients in the IVIG group also had a reduction in the volume and number of T2- and gadolinium-enhancing lesions ($P = 0.01$-0.03). Treatment was generally well tolerated.

In a second study, Sorenson and colleagues tested whether IVIG in combination with methylprednisolone facilitated the speed and degree of recovery from an acute MS relapse. Patients were randomly assigned to a single dose of either IVIG (1 g/kg) or placebo 24 hours before treatment, with 1 g/d IV methylprednisolone for 3 consecutive days. Both groups improved, but there was no significant difference between the IVIG and placebo groups in respect to the primary end point of the Expanded Disability Status Scale (EDSS).

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In a third study, a large, 2-year European, double-blind, placebo-controlled study of 318 secondary progressive patients (mean age 44 yrs, mean EDSS 5.24, mean percent of patients with a relapse/24 months prior to the study 51.7%). Patients were dosed with IVIG 1g/kg/month or placebo.

IVIG treatment had no beneficial effect on time to confirmed EDSS progression (hazard ratio, 1.11; [95% confidence interval 0.80-1.53] for IVIG vs placebo. The annual relapse rate was 0.46 for both groups. There was no significant difference between the treatment groups for other clinical outcome measures, including the change of T2-lesion load on brain MRI over time.

COMMENTARY

The use of IVIG in the treatment of MS remains controversial, with some neurological advocates, despite conflicting clinical efficacy data. Only 1 study above showed a modest benefit, ie, treating a patient presenting with a first demyelinating event with IVIG every 6 weeks for a year. However, in a similar first-attack study design using weekly interferon beta-1a, there was a substantially better reduction in clinical attacks and brain MRI findings (*N Engl J Med*. 2000;343:898-904). Thus, the routine use of IVIG for MS in these settings cannot be justified given the availability of other immunomodulatory therapies (interferon-beta, glatiramer acetate, natalizumab) that appear to more beneficial.

— **BRIAN R. APATOFF**

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High Homocysteine and Stroke: Cause or Effect?

ABSTRACTS & COMMENTARY

Synopsis: *The observed increase in risk of stroke among individuals homozygous for the MTHFR T allele is close to that predicted from the differences in homocysteine concentration conferred by this variant.*

Sources: Casas JP, et al. Homocysteine and Stroke : Evidence on a Causal Link From Mendelian Randomization. *Lancet.* 2005;365:224-232; Hankey GJ, et al. Homocysteine and Stroke. *Lancet.* 2005;365:194-195.

DATA FROM COHORT AND CASE-CONTROLLED STUDIES HAVE shown a positive, dose-related association between serum total homocysteine (tHcy) concentration and the risk of stroke.[1] Homocysteine concentration is related to smoking, blood pressure, existing atherosclerosis, and renal impairment. In addition, a stronger association between tHcy and stroke has been reported in retrospective studies in which researchers collected blood after stroke rather that in prospective studies, suggesting that acute stroke may increase tHcy. Therefore, whether raised tHcy causes stoke has not been established, and no randomized trial has shown that lowering tHcy reduces stroke risk.[2]

Casas and colleagues used Mendelian randomization to study the association between tHcy and stroke. They noted that individuals homozygous for a specific CT polymorphism of the methylene tetrahydrofolate reductace (MTHFR) gene have 20% higher tHcy concentrations (about 2 mol/L) than those with the CC genotype.[3] Therefore, they reasoned that if a higher tHcy concentration is pathogenetic, TT homozygotes (about 10% of the population) should be at increased risk of stroke.

Casas et al did a meta-analysis of 111 studies up to the end of 2003 that examined either the association between tHcy and MTHFR polymorphism and the risk of stroke (n = 13,928). They found that individuals homogeneous (TT) for the MTHFR polymorphism have a significantly higher tHcy (mean difference 1.93 mol/L) and a greater risk of stroke (odds ratio 1:26) than individuals who are homozygous (CC).

The observed increase in stroke risk among individuals homogeneous for the MTHFR T allele is close to that predicted from differences in tHcy concentration conferred by this polymorphism and, therefore, is consistent with a causal relation between tHcy concentration and stroke.

COMMENTARY

It is important to determine whether tHcy causes stroke because serum levels of tHcy can be lowered by the administration of folic acid and vitamins B6 and B12.[4] The association between tHcy and stroke described by Casas et al implies that lowering tHcy by 3 mol/L with vitamins should reduce the overall risk of stroke by about 20%. Nevertheless, the Vitamins in Stroke Prevention (VISP) trial reported that lowering tHcy by 2 mol/L with multivitamin therapy failed to prevent recurrent stroke.[2] As pointed out by Hankey and colleagues, VISP was statistically underpowered and could not exclude the possibility that vitamin therapy reduced relative stroke risk by up to 20%.

In addition, as pointed out by Casas et al, the effect of tHcy was small compared with those of the classic cardiovascular risk factors and, therefore, their results do not support routine screening of MTHFR genotype and tHcy concentration as a cost-effective means to detect individuals at risk for stroke. Furthermore, as Hankey et al stated in their editorial, even if tHcy is established as a cause of stroke, it may not be safe to prescribe long-term, high dose vitamins because of potential drug interactions and unknown biological effects.

Therefore, at the present time, clinicians can choose to administer vitamins to lower tHcy and/or recommend changes in lifestyle, pending the validation of vitamin therapy to prevent stroke and cardiovascular events by adequately powered randomized controlled trials. — **JOHN CARONNA**

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Do Autoantibodies Cause Narcolepsy?

ABSTRACT & COMMENTARY

Synopsis: *IgG from all narcolepsy patients significantly enhanced bladder contractile responses to the muscarinic agonist carbachol and neuronally released acetylcholine, as compared to the control IgG.*

Source: Smith A, et al. A Functional Autoantibody in Narcolepsy. *Lancet.* 2004;364:2122-2124.

THIS REPORT, FOR THE FIRST TIME, HAS IDENTIFIED a potential autoantibody which may play a role in narcolepsy. Narcolepsy-cataplexy appears to result from a deficiency of orexin (hypocretin) neurotransmission. Orexin is an excitatory neurotransmitter that promotes wakefulness and suppresses REM sleep. Evidence suggests that impaired orexin signaling causes both narcolepsy and cataplexy. Orexin-containing neurons originate in the lateral hypothalamus and have extensive projections to both cholinergic and monoaminergic brainstem nuclei. There appears to be reciprocal feedback from the brainstem nuclei into hypothalamic orexin-containing neurons. In addition, studies in neuroleptic dogs show central cholinergic hypersensitivity, which is linked to cataplexy. The ascending cholinergic pathways contribute importantly to arousal and maintenance of wakefulness.

Autoimmune mechanisms have, for a long time, been thought to be important in the development of narcolepsy. This is due to familial clustering, onset during adolescence, and a close association with HLA-DQB1*0602 allele. Initial attempts to identify neural autoantibodies in both canine and human narcolepsy, however, have been unsuccessful.

In the present study, Smith and colleagues obtained serum samples from 9 patients with narcolepsy and 9 healthy controls. All the narcolepsy patients were positive for HLA-DR2/DQB1*0602 and had marked daytime sleepiness. Seven patients had unequivocal cataplexy. Eight had abnormal REM-onset sleep, confirmed by multiple sleep latency testing. The human IgG was purified and then injected into mice. The mice received injections of 10 mg of IgG on 2 consecutive days. They were then sacrificed in 2 detrusor muscle strips per mouse, which were tested for contractile responses to electrical field stimulation and to the muscarinic agonist carbachol. Smith et al observed that IgG from all narcolepsy patients significantly enhanced bladder contractile responses to the muscarinic agonist carbachol and neuronally released acetylcholine, as compared to the control IgG. They examined sympathetically innervated vas deferens as a control, and there was no alteration in its response.

COMMENTARY

These studies are the first to identify the possibility of an autoantibody in narcolepsy. It is possible that it functions similar to the antithyroid-stimulating hormone receptor antibody, which occurs in Grave's disease. It appears to be difficult to detect

in serum, using conventional techniques. Smith et al's technique is very sensitive in picking up autoantibodies, however, the precise mechanism by which they increase cholinergic neurotransmission is not clear. It is also not yet known whether these autoantibodies will cross the blood brain barrier and result in increased cholinergic neurotransmission. If they were to do so, it might eventually lead to downregulation and damage to the ascending cholingeric pathways involved with arousal and wakefulness, which originate in the brainstem and, thereby, produce daytime sleepiness. These studies, however, do support the hypothesis that autoimmunity plays a role in the pathophysiology of narcolepsy. Identification of the neural target could lead to new possibilities for diagnosis and treatment of this disabling disease. — **M. FLINT BEAL**

Extraocular Muscle Susceptibility in Neuromuscular Disease

ABSTRACT & COMMENTARY

Synopsis: *EOMs have fundamentally distinct structural, functional, biochemical and immunological properties compared to other skeletal muscles. While these properties enable high fatigue resistance and the rapid and precise control of extraocular motility, they might also explain why EOMs are selectively involved in certain disorders, such as chronic progressive external ophthalmoplegia (CPEO), myasthenia gravis, and Graves' ophthalmopathy.*

Source: Yu Wai Man CY, et al. Extraocular Muscles Have Fundamentally Distinct Properties That Make Them Selectively Vulnerable to Certain Disorders. *Neuromuscular Disorders* 2005;15;17-23.

EXTRAOCULAR MUSCLES (EOM) ARE PREFERENTIALLY involved in a number of neuromuscular disorders. Several factors possibly contribute to this phenomenon. Compared to skeletal muscle fibers that are simply classified as either Type I (slow twitch, fatigue resistant) or Type II (A-fast twitch, fatigue resistant, and B and X- fast twitch, fatigable), EOMs are more complex. Classified into 6 types, based on color, location, and innervation, they include 1) orbital singly innervated fibers, 2) orbital multiply innervated fibers, 3) global red singly innervated fibers, 4) global intermediate singly innervated fibers, 5) global pale singly innervated fibers, and 6) global multiply innervated fibers. Whereas skeletal muscle cells invariably have a single axon innervation, 2 types of EOMs (orbital and global, multiply innervated fibers (MIFs)) have en-grappe endplates arising from several nerve fibers, allowing for a tonic, slow, and graded mode of contraction. This slowly increases muscle tension, causing contraction at the 2 ends of the muscle fiber, rather than at the muscle belly. Global MIFs only contract in the tonic mode, but orbital MIFs contract at both ends, as well as at the muscle belly. Unlike skeletal muscle that has a high safety factor built into the end plate potential, EOM twitch fibers have a smaller safety factor, and this may contribute to their vulnerability in myasthenia.

Motor units are smaller in the eye than in limb muscles, comprising 13-20 muscle fibers/motor neuron, compared to 100-2000 in the latter. Firing frequencies are 4-fold higher in the former, perhaps explained by their high expression of fast myosin heavy chain isoforms. Additionally, almost every EOM motor unit can participate in eye movements, compared to the recruitment principles in limb muscles. These factors engender greater energy demands in EOMs that are addressed by their higher mitochondrial content and blood flow, and may explain why EOMs are preferentially affected in neuromuscular disorders.

COMMENTARY

In contrast, EOMs are spared in muscular dystrophy, despite sharing the same molecular deficiency as skeletal muscle. Mechanical stability at the sarcolemma is attributed to the dystrophin-glycoprotein complex, which links intracellular and extracellular matrix proteins to produce scaffolding that maintains cell integrity. Mice with limb girdle muscular dystrophy consequent to deficiency of sarcoglycan maintain intact EOMs, despite involvement of limb and diaphragm muscles (*Neuromuscular Disorders.* 2000:11:197-207). Accessory ocular muscles including the levator palpebrae superioris and retractor bulbi (responsible for posterior displacement of the eye) were affected to a degree intermediate between the EOMs and limb muscles, demonstrating modestly increased numbers of centrally nucleated muscle fibers without evidence of

muscle necrosis, compensatory hypertrophy, or accumulation of adipose or fibrotic tissue in the endomysium. Despite secondary displacement of EOM and sarcoglycan by the sarcoglycan deficit, no functional abnormality was evident. How EOMs remain above the fray, despite sharing the mutational abnormality, remains an enigma. — **MICHAEL RUBIN**

Anti-MAG or Not?

ABSTRACT & COMMENTARY

Synopsis: *Pure sensory clinical phenotype, low median and ulnar terminal latency index, and absence of M responses in the lower limbs were significantly associated with the diagnosis of MAG-PN, and indicate a moderate to large increase in probability of this diagnosis in patients with chronic dysimmune demyelinating polyneuropathies.*

Source: Isoardo G, et al. Differential diagnosis of chronic dysimmune demyelinating polyneuropathies with and without anti-MAG antibodies. *Muscle Nerve*. 2005;31:52-58.

CAN ONE, AT THE INITIAL PATIENT ENCOUNTER, clinically differentiate chronic inflammatory demyelinating polyneuropathy (CIDP) from demyelinating neuropathy associated with anti-MAG antibodies (MAG-PN)? To answer this question, 35 CIDP patients and 14 with MAG-PN were examined by a blinded neurologist, and clinical findings and nerve conduction studies were analyzed to determine distinctive characteristics. Electrodiagnostic studies included study of bilateral median, ulnar, tibial, and peroneal motor nerves, and sural, ulnar, and median sensory nerves. Diagnosis of CIDP followed standard criteria (*J Neurol Sci.* 2000;173;129-139), with exclusionary criteria encompassing evidence of hereditary neuropathy, hypothyroidism, vitamin deficiency, vasculitis, amyloid, Refsum's disease, central nervous system white matter disease, optic atrophy, or retinitis pigmentosa. MAG-PN was confirmed by both IgM paraproteinemia and anti-MAG antibody assay > 1:13,000 using immunoblot. Most patients (n = 43) underwent spinal fluid analysis. Chi-square and Fisher's exact test, Student's t-test, the Mann-Whitney U-test, and Spearman's correlation coefficient provided statistical analysis.

Significant associations with MAG-PN included pure sensory neuropathy ($P = 0.008$), distal acquired demyelinating symmetric neuropathy (DADS) with no proximal weakness ($P = 0.04$), reduced median and ulnar terminal latency index ($P < 0.0001$) calculated as distal conduction distance (mm) / conduction velocity (m/s) X distal motor latency (ms), and unobtainable motor responses in the legs ($P = 0.001$). Incidence of conduction block on nerve conduction studies did not significantly differ between groups. None of the MAG-PN patients experienced a subacute onset, compared to 62.8 % (n = 22) of the CIDP group ($P < 0.0001$). Anti-MAG assays are likely to be positive in patients with the phenotypes noted, but the cost-effectiveness of this approach remains to be determined.

COMMENTARY

Anti-MAG antibodies bind to molecules in both the central (CNS) and peripheral nervous system (PNS), but with considerable variation. Sera from 18 patients, 12 men and 6 women, with IgM paraproteinemia, anti-MAG antibodies, and neuropathy was tested for immunoreactivity to myelin in the CNS and PNS by ELISA and Western blot analysis (*J Neurol Sci.* 2003;207;43-49). Indirect peroxidase staining on cryostat sections of sural nerve was also used to examine IgM binding to nerve. MAG was detected in central myelin by all the sera on Western blot, by peroxidase immunoreactivity in myelin sheaths in 12 sera, and by Western blot in peripheral myelin in 8 sera. Staining patterns in sural nerve varied. Some showed staining of the whole cross section of the myelin sheath (n = 8), others (n = 4) showed staining in 50% of fibers, while 6 showed no myelin sheath staining whatsoever. Of these last, 5 stained the outer border of the nerve fibers. Anti-MAG IgM ELISA titers closely correlated with both immunostaining patterns of the whole myelin sheath and with PNS-Western blot results, but PNS and CNS Western blot concordance was only 44.5%. Severity of neuropathy did not significantly correlate with ELISA titers, Western blot analysis, immunostaining patterns, or IgM level. CNS and PNS MAG may differ in their glycosylation patterns explaining the antibody binding differences in CNS and PNS myelin. How this impacts on the pathogenesis of demyelinating neuropathy remains to be elucidated. — **MICHAEL RUBIN**

Primary Generalized Dystonia: Encouraging Results For Deep-Brain Stimulation

ABSTRACT & COMMENTARY

Synopsis: *The findings support the efficacy and safety of the use of bilateral stimulation of the internal globus pallidus in selected patients with primary generalized dystonia.*

Source: Vidhailet M, et al. Bilateral Deep-Brain Stimulation of the Globus Pallidus in Primary generalized Dystonia. *N Engl J Med.* 2005;352:459-467.

THIS PROSPECTIVE, CONTROLLED, MULTICENTER study evaluated safety and efficacy of bilateral deep brain stimulation (DBS) of the ventral internal globus pallidus (GPi) in 22 patients with disabling and longstanding primary, progressive, generalized dystonia. Median age at surgical intervention was 30 years (range 14-54), median disease duration was 18 years (range 4-37), and 20 were receiving medical treatment for dystonia (14 taking anticholinergic agents). Seven patients carried the DYT1 mutation. All but 1 patient underwent postoperative MRI, confirming adequate electrode-contact position. Primary outcome measures were scores on movement and disability subscales of the Burke-Fahn-Marsden scale (BFMS), a validated instrument to assess dystonia severity. Assessments were performed preoperatively (baseline) and at 3, 6, and 12 months. Blinded raters evaluated videotaped, standardized BFMS examinations presented randomly, and patients served as their own controls. Secondary outcome measures included scores, with stimulators on and off at 3 months and quality of life at 12 months. At 12 months, BFMS movement score improved by >50% ($P < 0.001$), compared to baseline. Scores in a subset of individuals improved with time, with 14/22 improved by >50% at 12 months, compared to 11/22 at 3 months. Clinical improvement was attributable to DBS; turning off the stimulator at 3 months led to worsened dystonia within hours. Global disability score improved at month 3. Of the 14 taking anticholinergic medications preoperatively, mean dose was reduced by month 12. Five complications affected 3 patients: 1 patient experienced asymptomatic frontal lobe edema and other adverse events were hardware-related (lead fracture, scalp necrosis, hematoma, infection); all of these resolved without permanent effect.

COMMENTARY

Generalized dystonia is a chronic, progressive, heterogeneous disorder, typically affecting children and young adults. Treatment is often challenging. Its medical therapy commonly requires polypharmacy, with slow and painstaking dose adjustments, and drug side effects limit potential benefits. Botulinum toxin injections are impractical (in contrast to focal or segmental disease), given the number of muscles are involved. Surgical treatment of dystonia, exploiting DBS technology, was approved by the FDA in April 2003. However, reports in the literature are based on small case series or isolated cases, mostly without controls. The current study is important in 2 respects: 1) patient selection and treatment was highly standardized and 2) blinded assessments, on and off stimulation at 3 months, provided an important internal control. The study demonstrates that bilateral GPi DBS was effective in these severely impaired, carefully selected individuals up to 12 months after surgery. The exact neurophysiology of this observation remains speculative.[1,2] However, GPi neurons fire irregularly with reduced overall rates in dystonia, so presumably, DBS jams this abnormal signal. Most fascinating in the present study is the heterogeneous response of individuals, with 4/22 failing to improve. Indeed, overall improvement in scores seemed to be driven by subjects with diffuse, phasic hyperkinetic movements, as opposed to those with tonic postures. There is clearly a need for further refinement of criteria for patient selection for surgery. In parallel to our experience with DBS for Parkinson's disease, this step will no doubt be crucial in improving outcomes in this potentially devastating disorder. — CLAIRE HENCHCLIFFE

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Surgery For Epilepsy: Stratifying Outcome in Patients With Hippocampal Sclerosis

ABSTRACT & COMMENTARY

Synopsis: *Epilepsy duration is the most important predictor for long-term surgical outcome.*

Source: Jansky J et al. Temporal lobe Epilepsy With Hippocampal Sclerosis: Predictors For Long-Term Surgical Outcome. *Brain.* 2005;128:395-404.

Surgery for medication-resistant seizures is an increasingly utilized treatment option. Temporal lobectomy (either en bloc or tailored) is the most common surgical procedure in cases of idiopathic epilepsy involving complex partial seizures (with and without secondary generalization) of temporal lobe onset. Hippocampal sclerosis (HS) is identified in most of these cases, either by pre-operative MRI scan or microscopic analysis of resected tissue. While the presence of HS statistically predicts a favorable surgical outcome, it is clear that HS, as currently defined, is not the sole determinant of surgical outcome. Different patients can have disparate post-operative seizure frequencies, despite the fact that hippocampal pathology is essentially identical.

Jansky and colleagues posed the question of what other factors may play a role in determining surgical outcome in patients operated on for HS, as the apparent cause of their seizures. Specifically, they analyzed 171 surgical patients from the epilepsy surgery center located in Bielefeld, Germany. All patients had undergone a pre-surgical evaluation including video-EEG to localize ictal onset. All had HS by MRI scan and had undergone temporal lobectomy. Seizure-free outcome was assessed at 6 months and 2, 3, and 5 years after surgery. Not all patients were available for the full follow-up period.

Surgical outcome was correlated relative to the following clinical parameters: age at operation, gender, age at epilepsy onset, duration of epilepsy, history of febrile seizures, seizure frequency, presence of secondary generalized tonic-clonic seizures (GTCs), frequency of secondary GTCs, history of status epilepticus, ictal limb dystonia, post-ictal aphasia, unilateral interictal discharges, presence of contralateral ictal electrographic patterns, and standard en bloc temporal lobectory versus tailored resection. No other structural abnormalities were analyzed, save that patients with bilateral HS or other dual pathology were excluded from analysis.

In a multivariate analysis of the longer term outcomes, Jansky et al found the following factors to be independent predictors of poor outcome: at 2 years-secondary GTCs and ictal dystonia; at 3 years-ictal dystonia along with longer epilepsy duration; at 5 years-longer epilepsy duration ($P = 0.003$).

COMMENTARY

While there are methodological considerations that confound definitive analysis (eg, lack of homogeneity in the post-operative use of anti-epileptic drugs), these results are important because they again support the concept that earlier surgical treatment provides the greatest benefit in terms of long-term seizure freedom in the medically intractable epilepsy population (*N Engl J Med.* 2001;345:311-318).

The fact that the prognosis for 2-year outcome is influenced by the presence of secondary GTCs and ictal limb dystonia, may reflect the fact these phenomena result from electrographic ictal spread. This, in turn, could lead to the generation of new ictal foci. Unfortunately, since there are no data presented regarding the outcome of patients at 5 years who had had negative outcomes at 2 years, we do not know whether new foci exist and, if they do, whether they persist (leading to poor 5-5year outcome). Alternatively, new ictal foci may eventually extinguish (ie, running down is a term used to describe patients who have a more gradual reduction in seizure frequency for months to years post-operatively), which may be due to lack of reinforcement from the excised ictal focus.

We continue to await the results of the NIH-sponsored prospective study comparing best medical treatment vs early epilepsy surgery. Until then, with supporting evidence from multiple sources, we will continue to make early referrals for at least pre-surgical evaluation. — **ANDY DEAN**

CME Questions

9. Which of the following are true?
IVIG treatment in MS has been beneficial in the following setting(s):

a. acute relapses
b. secondary progressive MS
c. first demyelinating event
d. A and C

10. The risk of stroke in individuals homogeneous (TT) for the MTHFR gene polymorphism is increased by:

a. 0%
b. 5%
c. 20%
d. 50%
e. 100%

11. Choose the correct statement

a. Extraocular muscles (EOMs) are complex and usually classified into 8 types.
b. Limb muscles are classified into 6 types.
c. Extraocular muscles (EOMs) can be spared in muscular dystrophy despite sharing the same molecular deficiency as limb muscles.
d. Individual muscle fibers are always supplied by a single nerve fiber.
e. Motor units are smaller in the eye than in limb muscles, comprising 3-10 muscle fibers/motor neuron, compared to 100-2000 in the latter.

12. Demyelinating neuropathy associated with anti-MAG antibodies

a. tends to be predominantly sensory.
b. usually shows no proximal weakness.
c. demonstrates unobtainable motor responses in the legs on nerve conduction studies.
d. is usually not subacute in onset.
e. All the above are true

Answers: 9. (c); 10. (c); 11. (c); 12. (e)

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The Risk of Aspirin Withdrawal in ACS Patients

Stopping aspirin may be hazardous to your health, according to recent research. Patients with heart disease who developed acute coronary syndrome (ACS) were questioned to determine whether their aspirin therapy had recently been interrupted. Thirteen percent of patients with recurrent ACS had stopped aspirin within the previous month. The incidence of ST-segment elevation ACS was higher in those who stopped aspirin, compared to those who did not stop aspirin (39% vs 18%; *P*=0.001). The risk of stopping aspirin was particularly high for patients who had uncoated stents. The mean delay between aspirin withdrawal and acute coronary event was 10 days. Patients withdrew from aspirin for a number of reasons including minor surgery, endoscopy, dental treatment, bleeding, and noncompliance. The authors conclude that aspirin withdrawal in patients with coronary disease represents a risk for the occurrence of a new coronary event (*J Am Coll Cardiol.* 2005;45:456-459). The risk of ischemic stroke may be as much as 3 times higher with interruption of aspirin therapy, according to presentation at the International Stroke Conference. Researchers from Switzerland noted that the odds ratio for stroke or TIAs associated with aspirin discontinuation was 3.25 (95% CI). Seventy-seven percent of ischemic strokes related to aspirin discontinuation occurred in the first 8 days after aspirin was stopped, with remaining strokes occurring from day 9 to day 30. The reasons cited for discontinuing aspirin were primarily minor bleeding and minor surgical procedures—many of which can safely be performed (many dental procedures, cataract surgery among others) while patients are taking aspirin (strokeconference.americanheart.org /portal /strokeconference/sc/02.02.05c).

Neuropsychiatric Symptoms of Dementia

Treatment of neuropsychiatric symptoms in patients with dementia represents one of the biggest challenges in primary care. Dementia is diagnosed by the loss of cognitive function, but other symptoms are often more prominent including agitation, aggression, delusions, hallucinations, repetitive vocalizations, and wandering, among others. Many classes of psychiatric medications are used to treat neuropsychiatric symptoms in dementia including antidepressants, anxiolytics, anticonvulsants, cholinesterase inhibitors, typical antipsychotics, and atypical antipsychotics. Often these drugs are used in combination, and the cocktail can get confusing and even dangerous for patients and caregivers alike. A new review of the topic in the "Clinician's Corner" section of the February 2nd *Journal of the American Medical Association* helps clarify treatment options. The authors reviewed 29 articles that met their inclusion criteria. Among typical antipsychotics, which

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include haloperidol, thiothixene, chlorpromazine, trifluoperazine, and acetophenazine, there was no difference in the efficacy among these drugs in treating neuropsychiatric symptoms. Haloperidol may be somewhat more effective for treating aggression but not agitation. Side effects including extrapyramidal symptoms and somnolence are common with these agents. Antidepressants, including the SSRIs, were also relatively ineffective, except for treatment of depression associated with dementia. The best evidence for efficacy was found in the atypical antipsychotic group, especially risperidone (Risperdal) and olanzapine (Zyprexa). These drugs were found to have a modest effect on agitation/aggression, hallucinations, and delusions. A higher risk of stroke was found in the most recent trial (prompting a "Dear Doctor" letter from Janssen in April 2003). The cholinesterase inhibitors group including galantamine (Reminyl), donepezil (Aricept), and rivastigmine (Exelon) were somewhat disappointing with regard to neuropsychiatric symptoms, with minimal improvement of questionable clinical benefit. Memantine, the relatively new N-methly-D-asparte antagonist was seen to improve cognitive and functional parameters, but also did not improve neuropsychiatric symptoms. The authors stress that the management of neuropsychiatric symptoms in dementia "should always begin with an assessment of the medical (eg, pain and delirium) and environmental causes of the behavior." They also recommend starting with a cholinesterase inhibitor if the patient is not already receiving one, because they are relatively well tolerated and may benefit cognition and function (*JAMA.* 2005;293:596-608).

FDA Actions

Pfizer has received FDA approval to market pregabalin (Lyrica) for the treatment of painful diabetic neuropathy and post-herpetic neuralgia, the 2 most common types of neuropathic pain. Pregabalin was shown to be effective in a company-sponsored study of 338 patients with a 1-5 year history of painful, diabetic, peripheral neuropathy who were randomized to receive the drug at 1 of 3 doses or placebo for 5 weeks. Patients in the 300 and 600 mg/day doses showed improvements in mean pain score vs placebo ($P = 0.0001$), but no improvement was seen at the 75 mg/day dose. The higher doses also resulted in improvements in weekly pain score, sleep interferes score, patient global impression of change, clinical global impression of change, and lifestyle surveys. The most common side effects were dizziness and somnolence (*Neurology.* 2004;63:2104-2110). Pregabalin is a 3-substituted analogue of gamma-amino butyric acid (GABA), and is closely related to Pfizer's gabapentin (Neurontin), which recently lost its patent and is now available as a generic. Pregabalin is currently under review by the FDA for the treatment of partial seizures.

The FDA has also approved palifermin (Kepivance-Amgen) to decrease the incidence and duration of severe oral mucositis in patients with hematologic malignancies undergoing chemotherapy, with or without radiation, in preparation for bone marrow transplantation. The drug, which is the first agent to be approved for this indication, stimulates epithelial cell growth in mucous membranes. It is given prior to fractionated total body irradiation and high dose chemotherapy, and repeated after bone marrow transplantation. The drug's efficacy in non-hematologic malignancies has not been shown.

Citalopram (Celexa) is now available in generic tablets and liquid. The liquid formulation recently joined the tablet formulation for the popular SSRI antidepressant.

Extended release buproprion (Wellbutrin SR) is now available as a generic in the 200 mg strength.

Fosinopril/HCTZ (Monopril) has also joined the generic ranks in 10/12.5 mg and 20/12.5 mg strengths.

The FDA has also approved a generic fentanyl transdermal system (Duragesic) for the treatment of severe chronic pain. The new generic, which is produced by Mylan technologies, provides a constant dose of the drug for 72 hours.

Canada has suspended marketing of Adderall and Adderall XR because of reports of sudden unexplained death (SUD) in children taking the drugs. SUD has been associated with amphetamine abuse and has been reported in children with heart disease taking prescribed doses of amphetamines, including Adderall and Adderall XR. These latest reports of SUD have been in children without structural heart disease who were taking the drugs as prescribed. The FDA is looking at these reports, but “does not feel that any immediate changes are warranted in the FDA labeling or approved use of this drug.” More information is available on the FDA web site at FDA.gov.