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NEUROLOGY ALERT®

A monthly survey of developments in neurologic medicine

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Uncertain Role of Herpesvirus Infection in Multiple Sclerosis

ABSTRACTS & COMMENTARY

Sources: Ablashi DV, et al. Human Herpesvirus-6 (HHV-6) infection in multiple sclerosis: A preliminary report. *Multiple Sclerosis* 1998;4:490-496; Dockrell DH, et al. Human Herpesvirus 6. *Mayo Clin Proc* 1999;74:163-170; Ross RT, et al. Herpes zoster and multiple sclerosis. *Can J Neurol Sci* 1999;26:29-32.

National media attention has recently been drawn to the possible role of human herpesvirus-6 (HHV-6) in multiple sclerosis (MS), and consequently, neurologists have been barraged by anxious patient inquiries about being tested and treated for "the virus that causes MS." In fact, several reports over the past four years have sought to strengthen the relationship of HHV-6 in MS. (See *Neurol Alert* 1996;14:51-52; *Neurol Alert* 1997;16:14; *Infect Dis Alert* 1998;17:65-66.)

In a small study presented at the recent ANA meeting (Knox K, et al. *Ann Neurol* 1998;44:485A), three of eight MS patients showed evidence of active HHV-6 in the blood, and active HHV-6 could be found in the brain (7 of 10) or lymphoid (6 of 9) tissues of MS patients, but rarely in controls. Other reports by Ablashi and associates (and previously by Soldan SS, et al. *Nat Med* 1997;3:1394-1397) have suggested an increased incidence of IgG and IgM antibodies against certain HHV-6 antigens in the CSF and serum of MS patients compared to controls. Similarly, HHV-6 was more likely to be detected by PCR DNA amplification or isolated by culture in the blood or CSF of MS patients. Not all investigators, however, have found a correlation of HHV-6 with MS, in that in some studies the virus was detected as commonly in controls as in MS patients (e.g., Mayne M, et al. *Ann Neurol* 1998;44:391-394).

A review of HHV-6 by Dockrell and associates provides a perspective on the clinical biology and epidemiology of this ubiquitous virus. As with other human herpes viruses, (e.g., varicella zoster [VZV], Epstein-Barr virus [EBV], and cytomegalovirus [CMV]), HHV-6 is a common virus, with most patients being infected early in childhood. Occasionally the primary infection is manifest as fever

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and an erythematous rash (roseola infantum). Thus, virtually all persons with or without MS are infected and will have a "positive" HHV-6 IgG serology and, often, latent virus detectable by sensitive PCR methodology. A causal relationship of HHV-6 with MS may be difficult to make, and hinges on the distinction that MS patients are more likely to have reactivated virus in their blood or central nervous system.

Many clinicians have described in the literature that a variety of human herpesvirus infections such as HSV, EBV, and CMV can trigger inflammatory, demyelinating events in patients (e.g., see Apatoff BR. *Neurol Infect Epidemiol* 1997;2:99-102). Ross and associates studied the epidemiology of herpes zoster (HZ, caused by VZV, or HHV-3) in 633 Canadian MS patients, in which there was a 16.8% positivity rate of HZ, compared to 5.4-6.8% of control groups. HZ occurred at an earlier age in the MS group, with the majority of male patients having HZ prior to a diagnosis of MS. This history of HZ preceding MS is important, as corticosteroids or other immunosuppressive therapy could increase the HZ in the MS population.

COMMENTARY

Thus, the potential role of HHV-6 as a specific cofactor in MS needs to be further defined. HHV-6 may be one of a variety of persistent herpesvirus infections contributing to the pathogenesis of the disease, either by direct cytopathic effects of virus, or by activation of the immune system, which targets both the virus and secondarily the central nervous system. It is possible that the benefit of interferon-beta therapy in controlling MS disease activity may be by an antiviral effect. However, there is no convincing evidence that antiviral drugs against HHV-6 are an effective treatment for MS. Those drugs, ganciclovir and foscarnet, have considerable toxicity, require IV administration, and will require careful testing in controlled studies to determine safety and efficacy. One pilot study for MS patients with severe refractory disease is currently under way at New York Hospital-Cornell Medical Center. HHV-6 is relatively resistant to acyclovir and the related oral antivirals valacyclovir and famcyclovir, and their casual use as a treatment for MS cannot be supported at this time. A controlled trial of valacyclovir in relapsing MS is now being conducted at Rockefeller University by Drs. John Zabriske and Jacqueline Friedman. **—ba**

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MRI Abnormalities in Vitamin B_{12} Deficiency Myelopathy

ABSTRACTS & COMMENTARY

Sources: Katsaros VK, et al. MRI of spinal cord and brain lesions in subacute combined degeneration. *Neuroradiol* 1998;40:716-719; Locatelli ER, et al. MRI in vitamin B_{12} deficiency myelopathy. *Can J Neurol Sci* 1999;26:60-62.

Katsaros and colleagues describe a 60-year-old woman who presented with a gradual gait disturbance two months following a cholecystectomy, during which nitrous oxide was administered. She was unable to walk or stand without assistance, had a spastic ataxic paraparesis, with a right Babinski, and markedly reduced vibratory and position sense. There was a normal, slightly decreased Hgb and macrocytosis (13.1 g/dL, MCV 117.7), a low vitamin B_{12} "< 100 pg/mL," positive anti-parietal cell antibodies, and a normal cerebrospinal fluid exam. MRI analysis showed a continuous area of increased signal throughout the dorsal columns of the cervical spinal cord, with other scattered focal lesions in the brainstem and cerebellum. Following vitamin B_{12} therapy, the neurologic deficits improved such that she was walking independently by two months. The MRI abnormalities of the cervical cord only had resolved by four months.

Locatelli and colleagues report a 30-year-old woman

with an 18-month history of progressive paraparesis, trunk and limb numbness, and urinary and bowel incontinence. MRI of the spinal cord showed increased signal from C3-C8, in the posterior columns more than lateral, with gadolinium enhancement. The patient had a macrocytic anemia (Hgb 7.9 g/dL, MCV 123) with a vitamin B_{12} of 60 pg/mL (nL 200-1610). Intrinsic factor antibodies were positive. She was treated for vitamin B_{12} deficiency and hypothyroidism, with modest clinical improvement, but with resolution of MRI findings after 42 days.

COMMENTARY

Patients presenting with paresthesias and ataxic paraparesis regularly undergo MRI scanning of the spinal cord and brain, which often may reveal areas of high signal in the central nervous system. As indicated by the the above reports, severe vitamin B_{12} deficiency resulting in subacute combined degeneration of the spinal cord must also be considered in the broad differential diagnosis, in addition to multiple sclerosis, collagen-vascular disease, sarcoidosis, or other intramedullary lesions such as neoplasm. With a clinically significant low B_{12} level, the patient may have a corresponding elevation in the serum/urinary methylmalonic acid or homocysteine level, positive antiparietal cell/anti-intrinsic factor antibodies, and/or a macrocytic anemia. However, the best method to make an accurate diagnosis of cobalamin/vitamin B_{12} deficiency is a source of much medical controversy (e.g., see Green R. *Ann Int Med* 1996;124:509-511; Green R, Kinsella LJ. *Neurol* 1995;45:1435-1440; Healton EB, et al. *Medicine* 1991;70:229-244).

Potentially confusing the diagnostic interpretation of the MRI abnormalities and clinical presentation is the possibility of concomitant neurologic or systemic disease. For example, some patients with clinically definite multiple sclerosis have been shown to have low vitamin B_{12} levels, possibly on an autoimmune basis (see Reynolds EH, et al. *Arch Neurol* 1992;49:649-652). Similarly, patients with alcoholic disease of the nervous system can have a contributing nutritional B_{12} and folate deficiency. In the patients described above, one had been treated with nitrous oxide, which can inactivate cobalamins, and the other had autoimmune hypothyroidism.

Delay in the diagnosis and treatment of subacute combined degeneration is more likely to result in a residual clinical deficit. Prompt B_{12} supplementation, 1000 mcg/d injection for one week followed by monthly injections, may limit the extent of neurologic disability. **—ba**

Use of Tonsillar Biopsy to Identify the Variant Prion of Creutzfeldt-Jakob Disease

ABSTRACT & COMMENTARY

Source: Hill AF, et al. Investigation of variant Creutzfeldt-Jakob disease and other human prion diseases with tonsil biopsy samples. *Lancet* 1999;353:183-189.

The devastating, fatal encephalopathy of Creutzfeldt-Jakob disease (CJD), otherwise identified as prion disease, derives from the development of one of four pathologic isoforms of the body's normal cellular prion protein (PRPc). Each of the abnormal variables, inclusively designated as PRPsc, has been clinically and molecularly distinctly identified as: inherited, sporadic, acquired (e.g., iatrogenically or kuru) and, most recently, a variant form. (The four abnormal varieties differ in protein conformation and immunomolecular staining.) The variant form links to the British (and a single French case) epidemic of bovine spongiform encephalopathy (BSE). More important is that variant type 4 PrPsc can be selectively identified by western blotting and replicated by specimens drawn from a carrier's bodily lymphoreticular system. This tissue is apparently not consistent for harboring the other three variants. (Sheep scrapie prions also can be identified in lymphoreticular tissue.) Taking advantage of this singularity, Hill and colleagues examined tonsillar biopsy tissue in three autopsy brains and six presumed variant CJD cases. By random occurrence, they found variant prions in the intestinal appendiceal lymphoreticular system of one patient presenting with possible CJD. All patients were younger than 36 years of age and suspected of possible variant form of CJD. In the still alive group, behavioral and mood disorders were frequent, as were dysesthesias and signs of motor dysfunction. Dementia, however, marked all patients by the time that variant CJD was suspected. CSF protein 14-3-3, a relatively dependable diagnostic finding in the other forms of CJD, was positive in only five variant patients, while three other variant patients showed only traces.

Tonsillar biopsies in all nine variant patients were positive by western blotting for PrPsc, immunohistochemistry, or both. In five patients clinically suspected of variant CJD, tonsillar biopsy provided selectively accurate diagnosis of PrP on an average of 8.5 months preceding death. During the period of investigation, two out of five autopsies of CJD performed elsewhere in England revealed variant CJD prions. The remaining had sporadic

or iatrogenic CJD and showed neither western blot nor immunochemical identification of variant CJD.

COMMENTARY

This is a most important report. "Mad Cow" disease is due presumably to cattle innocently consuming remnants of contaminated offal from scrapie-affected sheep. The variant prion of CJD was discovered in humans in 1996, by which time most English and much Continental cattle had been sacrificed. Thus far, Hill et al indicate that 34 cases of variant prion disease have slowly become identified. That lymphoreticular tissue, easily obtained by tonsillar biopsy, has been found to contain the variant prion as early as 16 months before death is an important tool for early diagnosis. Hopefully, it also will catalyze greater and successful efforts to halt the progress of the clinical disease. **—fp**

Treating Erectile Dysfunction in Diabetic Men

ABSTRACTS & COMMENTARY

Sources: Rendell MS, et al. Sildenafil for treatment of erectile dysfunction in men with diabetes: A randomized controlled trial. *JAMA* 1999;281(5):421-426; Lipshultz LI, Kim ED. Treatment of erectile dysfunction in men with diabetes. Commentary. *JAMA* 1999;281(5):465-466.

Erectile dysfunction (ed) affects approximately half of American men (52%) between 40-70 years of age. Diabetics suffer from it at a significantly greater rate. At least one study indicates that 28% of diabetic males suffer complete erectile incapacity, a rate almost three times greater than in the general population. The immediate mechanisms of ED consist largely of impaired penile hemodynamic functions secondary to the damage of microvascular and microneural structures in the region. Normally, nitric oxide (NO) generated in the region triggers and sustains the erectile activities of these tissues.

Sildenafil (Viagra) taken orally in 50 or 100 mg tablets acts to increase NO activity in the corpus cavernosum, thereby enhancing erectile activity. Rendell and colleagues evaluated the drug's improvement in a double-blind study of 268 biologically matched diabetics with ED, ranging from 33-76 years of age. Following a four-week no-treatment phase, 132 randomized diabetic men were assigned to placebo and 136 were demographically matched to receive sildenafil. Approximately 80% of both the placebo and treated groups had type 2 diabetes.

The following averaged numbers emphasize the similar functional conditions of both the treated and nontreated numbers: age, 57 years (mostly 45-64); length of ED, 5.5 years; duration of diabetes, 12.1 years; type 2 diabetes, 81%; hypertension, 52%; ischemic heart disease, 26%; medications for hypertension, 54%; for cardiac, 12%; and antidepressants, 5%. Required were: stable, controlled diabetes for at least three months; plasma glucose level less than 300 mg/dL; and a stable female partner. Excluded were: patients with anatomic genital deformities; sexual disorders; severe psychiatric problems; serious systemic disease; severe hypertension; active diabetic retinopathy; severe autonomic neuropathy; diabetic ketoacidosis within 36 months; and regular use of nitrates.

Median length of treatment was 85 days for both groups. Median numbers of agent doses were 31 (range, 3-81) sildenafil and 25 (range, 2-83) placebo. Most treatment men (93%) took 100 mg sildenafil tablets, whereas 96% of the placebo patients took the largest available blank.

Outcomes at the 12-week termination of the study included the following: S = sildenafil receivers, P = placebo receivers. All quoted differences between S and P were significant at the $P < 0.001$ level.

1. Measurably improved erections: S = 56%.
2. Percent of successful erections during the last four weeks of treatment: S = 48%; P = 12%.
3. Numbers achieving at least one successful attempt at intercourse: S = 61%; P = 22%.
4. Ability to achieve erections at end of study compared with outset: S = 78%; P = 25%.
5. Functional improvement in maintaining erection at end of study compared to the start: S = 93%; P = 14%.

Adverse reactions occurred mainly among the sildenafil recipients as follows: transient headache 11%; dyspepsia 9%; mild respiratory symptoms 6%. Cardiac events occurred in 3% with sildenafil and 5% with placebo, but none were severe. Only 4% of the S group discontinued the drug vs. 8% in the P group.

COMMENTARY

Let's face it, erectile dysfunction and a number of other related sexual impairments are said to bring misery to more than half the American males older than age 40. Although many of the difficulties relate to psychiatric origins, neurological impairment with or without associated neuro-arteriolar disease contributes measurably to such patients' despair. Urologists have an important position in treating urinary tract and kidney diseases, but only a few have a strong knowledge of autonomic function/dysfunction and how to identify or approach the nervous system's visceral regulations. *Alert* urges neu-

rologists when consulting on or caring for adult males of any age to investigate sensitively the patient's sexual patterns and to evaluate their need for treatment. Rendell et al indicate that sildenafil can bring at least a measure of erectile effectiveness to males with diabetes, but this is pharmacologically just a start. Greater understanding of the pathophysiology of normal and abnormal erectile function along with the development of new treatments can derive from greater attention, ingenuity, and treatment by neurologists. **—fp**

Which of the following statements about sildenafil is *incorrect*?

a. The drug acts to maintain engorgement of the penile corpus cavernosum.
b. The drug induces successful erections as much as 4-5 times more than those achieved following placebo ingestion.
c. The drug should not be used for patients with hypertension or heart disease.
d. This study has shown the effectiveness of sildenafil as compared with blind placebo to be as much as six times greater.

Poorer Outcomes and Greater Costs Noted with Recurrent Stroke

ABSTRACT & COMMENTARY

Source: Samsa GP, et al. Epidemiology of recurrent cerebral infarction. A Medicare claims-based comparison of first and recurrent strokes on 2-year survival and cost. *Stroke* 1999; 30:338-349.

One of the main goals of acute and long-term management of stroke is to prevent its recurrence. Most physicians assume that recurrent strokes will leave patients with greater disability than first strokes, and that patients with recurrent strokes will have poorer outcomes, but no comprehensive study has established this as fact. Samsa and colleagues used a large, nationally representative cohort of patients to contrast 24-month survival and direct medical costs of first and recurrent strokes. From Medicare Provider Analysis and Review files, they selected a random 20% sample of 49,333 patients aged 65 and older who were hospitalized with a primary diagnosis of cerebral infarction during 1991. Of these, 90% had no record of a previous stroke and 10% had a record of at least one previous stroke. (*See Table.*)

Two-year survival from first stroke (56.7%) was significantly better than that for recurrent stroke (48.3%). The probability of surviving for at least two years after stroke was higher for women and for younger patients. Costs were similar for the initial hospital stay—although patients with recurrent stroke had longer stays than patients with first stroke by 0.7 days on average—and in months one to three after stroke. Thereafter, total costs were higher among recurrent stroke patients by approximately $375 per month across all patients, but the difference was greatest for younger patients, and least for patients aged 80 years or older. Most of the difference in cost was attributable to nursing home use (averaging approximately $150 per month) and acute hospitalization (averaging approximately $120 per month). Samsa et al conclude that to be accurate, decision and cost-effectiveness models should use different estimates of survival and cost outcomes for first and recurrent strokes.

Table

Characteristics of Patients with First or Recurrent Stroke

	Stroke	
	First	*Recurrent*
	(n = 44,386)	(n = 4947)
Age in Years (mean ± SD)	79 ± 8	79 ± 7
Men	40%	38%
White	85%	83%
Hypertension	34%	34%
Diabetes Mellitus	19%	23%
Myocardial Infarction	3%	3%
Congestive Heart Failure	12%	12%
Chronic Obstructive Pulmonary Disease	10%	9%
Valvular Heart Disease	2%	1%

COMMENTARY

Samsa et al found that patients with recurrent stroke have, on average, poorer survival, but higher costs than those with first stroke. In addition, they noted that patients with more than one previous stroke generally had worse outcomes than patients with a history of only one previous stroke, who, in turn, had poorer outcomes on average than patients with a first-ever stroke. These outcome patterns are consistent with the hypothesis that patients with recurrent strokes tend to have greater levels of mental and physical disability than those with first strokes. The relationship between chronic disability and higher costs is borne out by Samsa et al's observation that the cost of acute hospital treatment was similar in the two stroke groups, but that later costs were greater for recurrent stroke patients because of more nursing home stays and more hospitalizations.

The findings in this study can help public healthcare analysts to better estimate the true national economic burden of stroke. For clinicians, the study underlines the need for greater efforts on their part to prevent stroke by risk factor modification and to treat acute strokes, whether first or recurrent, vigorously to minimize the amount of brain damage and, hopefully, avert chronic disability. **—jjc**

The main reason there are greater costs involved with recurrent stroke patients vs. first strokes is:

a. longer initial hospital stay.
b. more frequent need for intensive care.
c. a longer period of early physical therapy.
d. more nursing home care.
e. a poorer survival rate.

The Cognitive Effect of the New Generation of Antiepileptic Drugs

ABSTRACT & COMMENTARY

Source: Martin R, et al. Cognitive effects of topiramate, gabapentin, and lamotrigine in healthy young adults. *Neurology* 1999;52:321-327.

Once the decision to initiate treatment with antiepileptic medications has been made, then one must ask which drug to add or substitute. The clinician must often balance the desired efficacy of a particular drug against its possible adverse cognitive effects. Many epileptic patients are cognitively impaired as a result of their illness and the cognitive effects of an antiepileptic medication may be obscured by a patient's pretreatment cognitive ability or confounded by an improvement in cognition due to improved seizure control. Martin and colleagues attempt to quantify the cognitive effects of the new antiepileptic medications, topiramate, gabapentin, and lamotrigine, by studying the effect of each medication in a population of normal, healthy young adults.

Martin et al evaluated a group of 17 healthy young adults and randomized each subject to receive one of the three drugs studied. To study the effects of acute dosing, each subject received a single dose of one of the three medications (topiramate 2.8 mg/kg in 6 subjects; lamotrigine 3.5 mg/kg in 5 subjects; gabapentin 17 mg/kg in 6 subjects). Cognitive effects of each medication were evaluated three hours after the acute dose by using a panel of cognitive tests that assessed sustained attention, psychomotor speed, memory, language, mood, and adverse effects. Lamotrigine and gabapentin induced no change in the subject's cognitive performance compared to baseline. Topiramate, however, induced a marked deterioration in language, with a 50% decline in verbal fluency and with a three-fold increase in error rate in a visual attention task. Similar effects were also seen following chronic dosing of each medication.

The cognitive effects of topiramate, gabapentin, and lamotrigine after chronic dosing were assessed over the course of a 30-day dose escalation period. Over this period, each subject received a progressive increase in dose to a predetermined target dose (topiramate 5.7mg/kg/d, lamotrigine 7.1mg/kg/d, and gabapentin 35mg/kg/d). Serum levels of each antiepileptic drug were measured at the end of 30 days; all were in the therapeutic range. Cognitive performance, omitting the early naming and fluency test, was assessed after two and four weeks of treatment using the tests used in the acute dosing phase. The subjects receiving lamotrigine and gabapentin again showed no impairment on cognitive testing compared to their pretreatment baseline. In fact, the subjects in the lamotrigine and gabapentin groups improved in visual attention tasks, which Martin et al attributed to practice effect. In contrast, subjects in the topiramate-treatment group showed worsened visual performance compared to baseline. The topiramate-treatment group also had a decline in verbal memory compared to baseline. Statistically significant differences in the verbal memory performance between each treatment group were not consistent at the two- and four-week assessments, but did favor lamotrigine and gabapentin over topiramate. Finally, the subjects receiving lamotrigine and gabapentin did not evidence any change in mood. The mood scores in the topiramate subjects, however, worsened; their subscale scores rating depression, confusion, and anger-hostility all worsened over the treatment period when compared to the pretreatment baseline scores.

COMMENTARY

Martin et al recognize the limits of their study, which include the small size of the group studied and the relatively rapid dose titration schedule used. Not discussed, however, is the method used to select the target doses for the three drugs studied. Differences in the relative doses taken may account in part for the observed cognitive effects. To be able to determine accurately the cognitive effects of the medications studied, dose response curves should be used. Martin et al concede that a slower escalation dose may also have reduced the incidence of side effects, but they note that lamotrigine, which is also best increased slowly, did not produce cognitive side effects when used in a similar titration schedule.

In choosing to test the cognitive effects of each drug in normal healthy adults, Martin et al have identified,

and partially quantified, the differential cognitive effects of each of the medications studied. They have not excluded subtle effects on cognition by each of the drugs tested, since a large study population may be necessary to resolve more subtle cognitive effects of each drug. Moreover, the effect in a population of epileptic patients may be less predictable than the effect in normal adults, since the effects of uncontrolled seizures, and the efficacy of each drug in controlling seizures, is purposefully not included in the present study. Though the study by Martin et al provides additional information to the clinician choosing an antiepileptic treatment, this decision ultimately rests on the clinical assessment of the patient's medical condition, expected response to treatment, and tolerability of anticipated side effects. **—fred a. lado & solomon l. moshé** (*Dr. Lado is EEG Fellow, Department of Neurology, Montefiore Medical Center-Albert Einstein College of Medicine, Bronx, NY. Dr. Moshé is Professor and Director, Pediatric Neurology and Clinical Neurophysiology, Department of Neurology, Montefiore Medical Center-Albert Einstein College of Medicine, Bronx, NY.*)

Which of the following drugs causes a worsening of visual attention and verbal memory after four weeks of use?

a. Topiramate
b. Gabapentin
c. Lamotrigine
d. Topiramate and lamotrigine
e. Topiramate, gabapentin, and lamotrigine

Clinical Updates

Distally Predominant Myasthenia Gravis

Source: Nations SP, et al. Distal myasthenia gravis. *Neurology* 1999;52:632-634.

From a retrospective chart review of 236 mg patients, Nations and colleagues noted nine (3%) with more pronounced distal than proximal muscle weakness. Finger extensors were most frequently affected, more so than distal leg or foot muscles. Three patients demonstrated distal weakness at onset, one after one month of ocular MG, and five after 3-45 years of disease. In patients with distally predominant muscle weakness, don't think of myasthenia until all other diagnoses are excluded. **—mr**

Plasma Exchange or Immunoglobulin for Myasthenic Crisis

Source: Qureshi AI, et al. Plasma exchange versus intravenous immunoglobulin treatment in myasthenic crisis. *Neurology* 1999;52:629-632.

Between 1990 and 1997, 54 patients with myasthenic crisis, defined as respiratory insufficiency with a forced vital capacity below one liter, negative inspiratory force below 20 cm H_2O, or requiring mechanical ventilation, were identified retrospectively from admission records of four university hospitals. Intravenous immune globulin (IVIG), 400 mg/kg/d for five days, had been administered in 26 cases, and plasma exchange (PE), five or six exchanges of 25-45 cc/kg each, was administered in 28. Cardiac, pulmonary, and hypertensive diseases were similar among the two groups and treatment selection was based on hospital preference.

At two weeks following initiation of treatment, significantly more PE patients were extubated (P = 0.02), and at four weeks, PE outcome was superior to IVIG. Fewer PE patients remained on a ventilator, none remained with a tracheotomy, and more patients had no disability (P = 0.04). PE patients experienced more complications (13 vs 5), comprising infections (n = 6), cardiovascular instability (n = 6), and coagulopathy (n = 1), with longer intensive care and overall hospital stays, but these differences were not statistically significant. PE appears to be preferable to IVIG for the management of myasthenic crisis with respiratory failure. **—mr**

Pregnancy and Myasthenia Gravis

Source: Batocchi AP, et al. Course and treatment of myasthenia gravis during pregnancy. *Neurology* 1999;52:447-452.

Sixty-four pregnancies among 47 myasthenia gravis (MG) patients, ages 19-39, were studied over a period extending from 1978-1997. Women were examined before, during, and after pregnancy. Those who were symptomatic received anti-cholinesterase (AChE) agents, prednisone or azathioprine if AChEs were inadequate, and plasmapheresis (PE), or intravenous immunoglobulin (IVIG) for myasthenic crisis. Anti-acetylcholine receptor binding antibodies (anti-AChR) were measured in mother and child, and repetitive nerve stimulation was performed on any child sus-

pected of neonatal myasthenia. Results were analyzed using chi-square and Mann-Whitney U tests.

Forty patients (85%) were anti-AChR antibody positive. Twenty women had mild MG (Osserman 2A), 25 severe MG (Osserman 2B, 3, and 4), and two had purely ocular disease (Osserman 1). Forty-four underwent thymectomy, 42 preconception and two postpartum. Of these, four showed thymoma, 35 had hyperplasia, and five had only normal/involuted thymus tissue.

Among women in remission, four of 23 (17%) developed mild MG during pregnancy and this was brought under control with AChEs alone. Among those with active MG on medication, approximately 40% either improved during pregnancy (n = 12), or remained unchanged (n = 13), while approximately 20% (n = 6) worsened. Four of the latter were mild in degree and were controlled with an increase in AChE dose alone, whereas two went into crisis, requiring high-dose prednisone, azathioprine, repeated PE and IVIG. Considering all completed pregnancies, 18.5% (n = 10) worsened during pregnancy, 60% in the first trimester (n = 6), 10% in the second (n = 1), and 30% in the third (n = 3). Postpartum, approximately 15% improved (n = 7) and 30% worsened (n = 15), the latter occurring immediately (n = 11) or within the puerperium (n = 4). Ten pregnancies aborted, six (induced) for psychosocial reasons, three (4.6%) spontaneously, with one ectopic pregnancy (1.5%). Of the 10 miscarriages, only one MG exacerbation resulted, following an induced abortion.

Four of 54 pregnancies delivered prematurely (7.4%), two each at 32 weeks and 35 weeks. Thirty percent overall were delivered by C-section (n = 16) and, collectively, 55 children were born to 43 MG women, with 9% (n = 5) premature and one, whose mother was on methotrexate up to a few months preconception, with multiple congenital anomalies. Approximately 50% of newborns assayed for anti-AChR antibody were positive but only 9% (5 of 55) demonstrated signs of neonatal MG, its occurrence not correlating with maternal AChR antibody positivity or titer. The course of MG during pregnancy is unpredictable and can change with different pregnancies, its long-term outcome is not worsened by pregnancy, its severity does not correlate with the occurrence of neonatal MG, and MG treatment may be safely administered to pregnant MG women.

COMMENTARY

What role do CD4+ and CD8+ T-cells play in the pathogenesis of MG is a classic unanswered question. Anti-acetylcholine receptor (anti-AChR) antibodies are IgG isotypes whose production is stimulated by helper T cells, but an AChR-specific helper T-cell effect has yet to be demonstrated (Hohlfeld R. *Neurology* 1999; 52:443-445). A series of elegant experiments by Wang and associates (Wang ZY, et al. *Neurology* 1999;52:484-497) may now provide some answers. Using severe combined immunodeficiency (SCID) mice, which lack mature T and B cells due to defective DNA-dependent protein kinase activity (Blunt T, et al. *Cell* 1995;80:813-823), a number of man/mouse models of MG were created by intraperitoneally engrafting the mice with lymphocytes from MG patients. These chimeric models were used to determine the role of CD4+ and CD8+ T-cells in symptomatic MG.

Using blood from the same MG patients, SCID mice were engrafted with one of the following: 1) blood lymphocytes (BL), 2) BL depleted of CD4+ T-cells, 3) BL depleted of CD8+ T-cells, 4) BL depleted of CD4+ T-cells but reconstituted with autologous CD4+ T-cells specific for AChR, or 5) BL depleted of CD4+ T-cells but reconstituted with autologous CD4+ T-cells specific for two unrelated antigens, tetanus and diphtheria toxoids. Myasthenic weakness and human AChR antibodies frequently developed in mice from experiments 1, 3, and 4, all of which included CD4+ T-cells, but not from experiment 2 or 5, which were depleted of CD4+ T-cells but included CD8+ T-cells. Muscle weakness did not always correlate with AChR antibody positivity, nor did antibody positivity predict weakness, but anticholinesterase agents could transiently reverse weakness when present. Presumably, highly pathogenic antibody is formed and binds to the receptor, thereby clearing the serum, resulting in weakness with the (apparent) absence of antibody. Mice engrafted with normal control serum neither developed MG weakness nor AChR antibodies. CD4+ T-cells particularly AChR-specific CD4+ T-cells but not CD8+ T-cells, appear necessary for the pathogenesis of MG weakness. **—mr**

Which of the following statements regarding myasthenia gravis is true?

a. For myasthenic crisis, outcome following treatment with plasma exchange appears superior to intravenous immune globulin with respect to ventilator dependency, continued tracheotomy, and disability at four weeks.
b. The course of myasthenia during pregnancy predictably worsens, but its long-term outcome is not worsened by pregnancy, nor does its severity correlate with the occurrence of neonatal MG.
c. Overall, 10% of MG patients present with more pronounced distal than proximal muscle weakness, with finger flexors most frequently affected, more so than distal leg or foot muscles.
d. CD8+ T-cells, particularly AChR-specific CD8+ T-cells but not CD4+ T-cells, appear necessary for the pathogenesis of MG weakness.