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Autoimmune Autonomic Neuropathies

A B S T R A C T & C O M M E N T A R Y

Source: Vernino S, et al. Autoantibodies to ganglionic acetylcholine receptors in autoimmune autonomic neuropathies. *N Engl J Med* 2000;343:847-855.

Immunoprecipitation assays with solubilized human neuroblastoma acetylcholine receptors and iodine-125-labeled epibatadine, the latter a high-affinity agonist of neuronal ganglionic receptors, were used to screen serum from 157 dysautonomia patients for ganglionic-receptor-blocking and binding antibodies, respectively. Patients diagnoses included idiopathic autonomic neuropathy (n = 28), paraneoplastic autonomic neuropathy (n = 18, 12 with small cell lung cancer), postural tachycardia syndrome (n = 15), idiopathic gastrointestinal dysmotility (n = 34), diabetic autonomic neuropathy (n = 18), pure autonomic failure (n = 24), multisystem atrophy, and nondiabetic sensorimotor and autonomic neuropathy (n = 10 each). These latter comprised Guillain-Barre syndrome, chronic inflammatory demyelinating polyneuropathy, hereditary sensory and autonomic neuropathy, and idiopathic small fiber neuropathy. Autonomic function tests used to diagnose dysautonomia, the Composite Autonomic Severity Scale (Low PA. *J Clin Neurophysiol* 1993;10:14-27), encompassed the quantitative sudomotor axon reflex test (QSART), heart rate response to deep breathing and Valsalva maneuver, blood pressure response to head-up tilt and Valsalva maneuver, the thermoregulatory sweat test, and gastrointestinal motility studies including intestinal transit and endoscopic manometry. Exclusionary criteria included Lambert Eaton syndrome, lack of objective evidence of dysautonomia, and insufficient data to diagnose the type of dysautonomia. Healthy subjects (n = 133), and 13 with gastrointestinal symptoms but normal motility studies, served as controls.

None of the 146 controls demonstrated detectable antibodies. Ganglionic-receptor-binding antibodies were detected in 25 (16%) dysautonomia patients, 19 (76%) of which had either idiopathic autonomic neuropathy (14/28, 50%), or paraneoplastic autonomic neuropathy (5/18, 28%). No patient with degenerative or non-diabetic dysautonomia expressed the antibody. Idiopathic (4/28, 14%) and

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paraneoplastic (3/18, 17%) autonomic neuropathy patients were positive for ganglionic-receptor-blocking antibodies which, however, were never found in the absence of binding antibodies. Higher antibody levels correlated with more severe autonomic failure as assessed by the Composite Autonomic Severity Scale and changing levels correlated with clinical status. Idiopathic and paraneoplastic autonomic neuropathies are immune mediated. Ganglionic-receptor-binding and blocking antibodies are predictors of these forms of autonomic neuropathy, and appear to play a role in their pathogenesis.

COMMENTARY

Complement-fixing sympathetic ganglia and complement-fixing vagus nerve autoantibodies are present in up to 40% and 13%, respectively, of Type 1 diabetics at diagnosis, compared to 5% and 0%, respectively, of healthy controls (Zanone MM, et al. *Diabetologia* 1993; 36:564-569; *Diabetes Care* 1997;1:1-4). Diabetics with autonomic neuropathy, diagnosed on the basis of severe diabetic diarrhea, gastroparetic vomiting, postural hypotension, and bladder paresis, are antibody positive more often than diabetics without autonomic neuropathy, 33% vs. 8%, respectively (Schsnell O, et al. *Diabetologia* 1996;39:970-975). Those with electrocardiographic-based cardiac autonomic neuropathy are also more likely to demonstrate complement-fixing sympathetic ganglia autoantibodies (9/22, 41%) than patients without cardiac autonomic neuropathy (3/26, 12%). Autonomic nervous tissue antibodies appear to play a role in the autonomic neuropathy of type 1 diabetes.

Autoantibodies do not appear to play a role in the pathogenesis of cardiac dysautonomia in type 2 diabetes. Among 127 type 2 diabetics, complement-fixing sympathetic and parasympathetic ganglia autoantibodies were detected in approximately 9% and 6% respectively, compared to 1% and 0% in normal controls. However, no significant difference in antibody levels was evident in diabetics with or without cardiac dysautonomia (Schnell O, et al. *Exp Clin Endocrinol Diabetes* 2000;108:181-186).

Significantly, in the absence of a hereditary small fiber neuropathy, dysautonomia should alert the neurologist to an acquired etiology. Only one of nine hereditary motor and sensory neuropathy type I patients (Charcot-Marie-Tooth disease, type I, HMSN I) demonstrated abnormalities on two or more autonomic function tests (pupillary reflexes, vasomotor control, baroreceptor reflexes, and sudomotor function), compared to three of three patients with Lambert Eaton syndrome and none of 33 controls. Dysautonomia is uncommon in HMSN I (Kalmijn S, et al. *Electromyogr Clin Neurophysiol* 1999;39:349-353). **—michael rubin**

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Thyroid Assessment in MS Patients on Interferon-Beta Therapy

ABSTRACTS & COMMENTARY

Sources: Monzani F, et al. Long term interferon-beta-1b therapy for MS: Is routine thyroid assessment always useful? *Neurology* 2000;55:549-552; Rotondi M, et al. Long-term treatment with interferon-beta therapy for multiple sclerosis and occurrence of Graves' disease. *J Endocrinol Invest* 2000; 23:321-324.

Monzani and colleagues studied 31 multiple sclerosis (MS) patients on interferon-beta therapy for three years with attention to onset and progression of thyroid disease. In the first year of treatment there was a 33% incidence of early thyroid dysfunction (both hypo and hyperthyroid), with a particularly high incidence (75%) in patients with baseline Hashimoto's thyroiditis. Many of these patients were clinically euthyroid with elevated anti-thyroid antibody titers.

Monzani and colleagues found that of the six patients who developed subclinical hypothyroidism in the first year, thyroid dysfunction persisted in only two. Monzani et al conclude that incident thyroid dysfunction typically occurs in the first year of interferon-beta treatment and is usually mild and transient. Regular monitoring of thyroid function tests was recommended in patients with baseline thyroid disease.

In a single case report, Rontondi and colleagues describe a 40-year-old MS patient who developed severe Graves' disease after 22 months on interferon-beta therapy, requiring methimazole and propanolol treatment despite discontinuation of interferon-beta.

An extensive literature describes thyroid dysfunction in patients receiving interferon-alpha for hepatitis C or hematological malignancies. MS patients in general also appear to have a slightly higher incidence of autoimmune thyroid disease. Thus, the finding of thyroid disorder in MS patients on interferon-beta treatment is not surprising, but in most cases it does not seem to contradict initiating or continuing interferon-beta. **—michael rubin**

Sumatriptan Provides Headache Relief in the Workplace

ABSTRACT & COMMENTARY

Source: Schulman EA, et al. Effectiveness of sumatriptan in reducing productivity loss due to migraine: Results of a randomized, double-blind, placebo-controlled clinical trial. *Mayo Clin Proc* 2000;75:782-789.

Migraine affects roughly 24% of the population and is most prevalent in individuals during the most productive years of their life. In fact, estimated labor costs due to migraine range in the billions to tens of billions of dollars. The efficacy of the triptans as an acute migraine abortive treatment has been well established. The benefit of using these medications to prevent work-related morbidity has been less well studied. Schulman and associates report the results of a multicenter, randomized, placebo-controlled, parallel-group trial comparing the benefits of 6 mg subcutaneous sumatriptan to placebo. Several outcome measures were used including: time to headache relief, number of patients returning to normal work performance two hours after injection and across the work shift, and time to return to normal work performance.

One hundred sixteen patients comprised the final study group. Seventy-six received sumatriptan and 40 took placebo. Ages ranged from 18-65 and occupations ranged across the employment spectrum with subjects only needing to work outside the home for a minimum of eight hours. Sumatriptan demonstrated clear efficacy in one-hour headache relief after injection compared to controls (48/76, 63% vs 13/40, 33%; $P = 0.004$). Additionally, sumatriptan was superior to control by any number of work-related efficacy parameters. The sumatriptan-treated group showed significant reductions compared to controls in productivity loss over the entire work shift (36.8 vs 72.6 minutes; $P = 0.001$). The sumatriptan-treated group experienced shorter return to normal work performance at two hours (53/76, 70% vs 12/40, 30%; $P < 0.001$) and across the eight hour shift (64/76, 84% vs 23/40, 58%; $P < 0.001$). Adverse events were minimal and there was no loss of work related to the use of sumatriptan.

COMMENTARY

The current study helps establish the relationship between the clinical efficacy of sumatriptan and work productivity. The study takes into account the importance of measuring the detrimental effect migraine can have in compromising work performance. Previous studies have looked at just absenteeism in migraine patients and have underestimated what Schulman et al call "presenteeism," or the impairment of work by migraineurs who continue to work at reduced capacity. Fiscally myopic insurers and employers ought to take notice that when it comes to migraine and the seemingly high cost of the triptan class of medications, effective treatment is money well spent. **—jeffrey reich**

Cardiac Headaches: Beware of the Rare

ABSTRACT & COMMENTARY

Source: Lanza GA, et al. Angina pectoris: A headache. *Lancet* 2000;356:998.

Lanza and colleagues report the case of a 68-year-old man in whom myocardial ischemia presented as headache. The patient had a three-year history of brief occipital headaches occurring at rest.

One week before admission to the hospital, his headaches increased in frequency. At that time, brain MRI, chest radiographs, electrocardiogram (ECG), and routine laboratory tests all were normal. Cardiovascular

risk factors included smoking and hypercholesterolemia.

On the day of admission, he reported a constant headache with pain in both shoulders. ECG was unchanged but serum levels of both CK-MB and cardiac Troponin I were elevated. Headache subsided after nitrates, ß-blockers, and aspirin were administered.

Two days later, during an exercise test, he reported typical headache symptoms concomitant with ECG abnormalities. Symptoms again were relieved by sublingual nitrates. He underwent coronary angiography and coronary artery bypass grafting of his left anterior descending and circumflex coronary arteries following which he remained headache free during three years of follow-up.

COMMENTARY

In this patient, the response of his headaches to nitrates, which more frequently cause headache rather than relieving it, was a clue to the myocardial cause of his occipital symptoms. Cardiac pain typically can be referred to areas besides the chest such as the neck, jaw, arms, and epigastrium (Meller ST, Gebhart GF. *Neuroscience* 1992;488:501-524). Headache as a symptom of myocardial ischemia is rare but has been reported previously (Lefkowitz D, Biller J. *Arch Neurol* 1982;39:130; Lipton RB, et al. *Neurology* 1997;49:813-816). The site of "cardiac headache" is not specifically occipital and can also be frontal, parietal, temporal, or vertex in location.

Physicians should consider a cardiac origin of headache when it is episodic, lasts only a few minutes, or is exercise-induced and relieved by rest, particularly in patients with cardiovascular risk factors. **—john j. caronna**

Apolipoprotein E Polymorphism

ABSTRACT & COMMENTARY

Source: Schiefermeier M, et al. Survival and neurological outcome after cardiopulmonary resuscitation. *Stroke* 2000; 31:2068-2073.

A number of factors contribute to ultimate neurological outcome following pathological asystole. The time that separates heart stoppage to resumption of circulation is paramount, as is whether the arrest occurred outside hospital walls or within. Normal apolipoprotein E 3/3 (apoE 3/3) functions as a major carrier of reparative cholesterol, cholesterol esters and nervous system lipids. It appears that apoE production continuously acts to the integrity of cell membranes. Variant alleles of the apoE 3/3 have been strongly associated with the advent of early Alzheimer disease as well as in worsening the injuries of brain trauma associated with boxing and road accidents. Schiefermeier and associates now report the comparison of neurological outcomes in patients undergoing cardiac asystole and genetically possessing either normal or abnormal variants of the apoE 3/3 gene.

Sixty-five men and 15 women treated at the University of Vienna Hospital suffered cardiac asystole lasting approximately 5-10 minutes with mean returns of spontaneous circulation at 20 minutes. Outcomes among these patients expressing apoE 3/3 (n = 47) compared to nonapoE 3/3 (n = 33) differed significantly. The following paragraphs list specific factors that 1) affected both groups, and 2) expressed differences between the normal and variant apoE groups.

Nonsignificant differences included: age in years; ratios of men or women; blood pH; plasma lactate; similar proportions of asystole time in hospital and without hospital; cardiac causes; cardiac ventricular fibrillation; asystole at onset; time to return to spontaneous circulation (mins); time to regain low cardiac blood flow; time to regain normal flow; and first meaningful reactivity of patients with apoE 3/3 5 ± 6 days compared to in non 3/3 group compared to 10 ± 10 days in the non 3/3 apoE (P = 0.06).

Table

Outcome for ApoE 3/3 vs. nonApoE 3/3

	ApoE 3/3	nonApoE 3/3
Good (n =)	26	9
Poor	21	24 (P = 0.013)
Survivors	30	11
Deaths	17	22 (P = 0.007)

The Table numbers above describe patients who experienced less than 20 minutes of cardiac arrest and regained spontaneous circulation within 60 minutes. Patients who experienced asystole within the hospital had 12.9 favorable outcome compared with those who suffered cardiac arrest outside the hospital. The table identifies only patients who recovered arrest in less than 20 minutes, whether in or outside of hospital.

Following the tabular calculations, Schiefermeier et al analyzed outcomes of patients carrying the apoE 3/4 or apoE 4/4 genotypes as well as those having apoE 2/3 or 2/2 genotypes. A total of 28% of the patients with the apoE 3/4 or the epoE 4/4 made a good recovery compared to the apoE 3/3 genotype's outcome of 55%

good. Among patients containing apoE 2/3 or 2/2, only 17% survived compared with the 64% survival of patients with the apoE 3/3 genotype. Numbers were too small to make strong probability of the observations.

COMMENTARY

As Schiefermeier et al comment, homozygosity for apoE 3/3 is the most common apoE isoform. They cite the well known association of abnormal forms of this apolipoprotein in the central nervous system. Alzheimer's disease, cerebral vascular morbidity, brain trauma, and intracerebral hemorrhage walk in its wake. Despite considerable effort, clear explanations of how and why variant genotypes of apoE 3/3 select their targets of vulnerability with different forms of morphological tissue injury. Accordingly, the specific effects in generating injuries to the brain remain not fully understood. **—fred plum**

Vitamins and Stroke Prevention: Is a Healthy Diet Good Enough?

ABSTRACTS & COMMENTARY

Sources: Yokoyama T, et al. Serum vitamin C concentration was inversely associated with subsequent 20-year incidence of stroke in a japanese rural community: The shibata study. *Stroke* 2000;31:2287-2294; Hirvonen T, et al. Intake of flavonoids, carotenoids, vitamins C and E, and risk of stroke in male smokers. *Stroke* 2000;31:2301-2306; Cherubini A, et al. Antioxidant profile and early outcome in stroke patients. *Stroke* 2000;31:2295-2300.

In this series of investigations, data suggest that vitamin intake may reduce the risk of ischemic or hemorrhagic stroke. Such benefits might be achieved from the dietary consumption of fruits and vegetables or they may be derived from the intake of exogenous vitamins. Furthermore, the particular relative effects of different vitamins are not well understood. Because LDL oxidation is an important and, possibly, a necessary step in the development of atherosclerosis, compounds with antioxidant properties, such as vitamin C or beta-carotene, may attenuate or arrest this process. Compounds such as vitamin E and flavinoids have been shown to reduce platelet aggregation. In addition, a moderate but significant drop in blood pressure, a major stroke risk factor, has been associated with vitamin C. Finally, the benefits of vitamin intake may depend on stroke pathophysiology. Subytpes of ischemic stroke, such as embolic or lacunar types, as compared to intracerebral hemorrhage, may show variable effects.

In a Japanese rural community, Yokoyama and associates report on a cohort of 880 men and 1241 women. Over a 20-year observation period, 196 strokes occurred (109 cerebral infarctions, 54 hemorrhages). Vitamin C intake was derived solely from dietary sources with no one in the cohort taking vitamin supplements. Higher serum vitamin C levels measured at baseline were associated with a decrease in stroke rates (odds ratios of 0.89, 0.72 and 0.59, for the second, third and fourth quartiles compared with the first; $P = 0.002$). This relationship applied separately to both ischemic stroke and ICH and was not reduced after corrections for stroke risk factors such as hypercholesterolemia. Although a weak inverse association between vitamin C levels and blood pressure was detected, this did not explain its benefit. Vitamin C remained protective for stroke even after correction for blood pressure.

Hirvonen and associates report results from the Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) study, a primary prevention, interventional trial among male smokers in Finland. Primarily designed to examine cancer rates, this cohort unexpectedly showed increased lung cancer rates among men taking beta-carotene supplementation. By contrast, in the present study, a follow-up report on the same population, intake of beta-carotene was favorable, associated with a decreased risk of ischemic stroke (relative risk [RR] 0.74). This remained significant in multivariate analysis. Other nutrients were also shown to have benefits. These were not supplemented, as beta-carotene, but rather intake was quantitated based on dietary questionnaires. Vitamin C was associated with a decreased risk of intracerebral hemorrhage (ICH; RR = 0.39), lutein plus zeaxanthin with fewer occurrences of subarachnoid hemorrhage (RR = 0.47), and lycopene with decreased incidence of both ischemic stroke and ICH (RR = 0.74 and 0.45, respectively). None of these remained significant in multivariate analyses. An increased intake of fruits and vegetables showed a protective effect against stroke, but this effect was attenuated when corrected for beta-carotene intake. Prior studies of flavonols, flavones, or vitamin E intake have shown variable results. None of these agents showed benefit in the ATBC study, either in isolation or in grouped analysis. In contrast to the Japanese cohort, intake of vitamin C had no effect on blood pressure.

In a related report, Cherubini and associates studied levels of antioxidant compounds (vitamin C, A, and E) and antioxidant enzymes (superoxide dismutase [SOD] and glutathione peroxidase) in the aftermath of stroke.

Cherubini et al hypothesized that levels of these agents would drop on the basis of oxidative stress. Indeed, patients showed lower vitamin C and A levels as well as plasma SOD activity when compared with controls. Also, decreased plasma levels of vitamin C were directly correlated with poorer functional outcome and neurological status. Vitamin levels returned to control levels at one week post-stroke. As Cherubini et al indicate, the maintenance of higher antioxidant activity post-stroke may lessen the effects of free radical mediated excitotoxic damage or prevent the potentially injurious effects of reperfusion.

COMMENTARY

These studies add to a growing body of evidence that antioxidant vitamins may prevent or reduce the adverse effects of stroke. A variety of putative mechanisms have been proposed. Despite these findings, however, a mandate for widespread supplementation as primary prevention is far from clear. Prior investigations of beta-carotene supplementation, such as the Physicians Health Study (Hennekens CH, et al. *N Engl J Med* 1996;334:1145-1149), showed a lack of benefit not only for prevention of neoplasms or cardiovascular disease but also for the specific endpoint of stroke. Both the ATBC and CARET study (Omenn GS, et al. *N Engl J Med* 1996;334:1150-1155) showed increased cancer rates in the setting of beta-carotene supplementation. Furthermore, as suggested by the Japanese study, natural dietary intake (in this case, of vitamin C) rather than supplementation may produce a reduction in stroke incidence. In the ATBC study, although dietary effects were perhaps clouded by supplementation, the suggestion remained that unknown dietary factors might affect outcomes, despite added vitamins. Until futher data comes forth, we should continue to heed the advice of our mothers, "Eat your vegetables, they're good for you." **—alan z. segal**

Chronic Deep Brain Stimulation in Parkinson's Disease

ABSTRACT & COMMENTARY

Source: Haberler C, et al. No tissue damage by chronic deep brain stimulation in Parkinson's disease. *Ann Neurol* 2000; 48:372-376.

Over the last five years, there has been an exponential increase in the number of patients with Parkinson's disease undergoing implantation of deep brain stimulators. Three main targets are available for stimulation: the thalamic ventral intermediate nucleus (VIM), the subthalamic nucleus (STN), and the internal globus pallidus. Currently, the VIM is the only target approved by the Food and Drug Administration (FDA) for implantation. However, as discussed previously in *Neurology Alert* (Frucht S. *Neurol Alert* 1999;18:15-16), the STN is increasingly being accessed as the target of choice, as chronic stimulation of this nucleus improves all of the cardinal features of dopa-responsive parkinsonism, including tremor.

COMMENTARY

Deep brain stimulation (DBS) was serendipitously discovered to produce clinical benefit when early stereotactic neurosurgeons stimulated potential targets prior to creating a surgical lesion. DBS offers several advantages to ablative surgery. The effects of stimulation are reversible, and DBS offers the opportunity to adjust the patient's stimulation parameters in order to obtain the maximum clinical benefit. DBS can be performed on both sides of the brain, whereas the risks of neurological or cognitive deficits from bilateral thalamotomy or pallidotomy are unacceptable. There may also be a slightly reduced surgical risk with DBS compared to surgery in which lesions are placed.

The mechanism by which DBS produces functional benefit is unknown. Application of electrical current has been postulated to interfere with or change the functional circuitry of the target nuclei and its connections. One major concern is that chronic DBS might injure or permanently damage the target nuclei. In this important paper, Haberler and colleagues report on eight Parkinson's disease patients who were implanted with DBS devices. Four patients underwent bilateral stimulation; in six, the VIM was targeted, and two underwent STN implantation. Stimulation was performed for up to 70 months. In all cases, death was unrelated to stimulation.

After removal of the stimulating electrodes, all brains were formalin-fixed, and the electrode tract and target nuclei were closely examined for evidence of gliosis, inflammatory reaction or neuronal loss. There was no evidence of damage to brain parenchyma in any patient.

These results are especially important given the number of patients who are likely to undergo implantation in the next decade. It should be noted, however, that only two STN patients were included in this series. It will be important to extend these observations in future studies to a larger cohort of STN patients. For now, though, DBS appears not only to be a superior alternative to ablative lesioning for patients with Parkinson's disease, but also to be safe as well. **—steven frucht**

Early Treatment Intervention in MS—Delaying Development of Subsequent Disease

ABSTRACTS & COMMENTARY

Sources: Jacobs LD, et al. Intramuscular interferon beta-1a therapy initiated during a first demyelinating event in multiple sclerosis. *N Engl J Med* 2000;343:898-904; Scott TF, et al. Short-term prognosis in early relapsing-remitting multiple sclerosis. *Neurology* 2000;55:689-693; Noseworthy JH, et al. Medical progress: Multiple sclerosis. *N Engl J Med* 2000;343: 938-104.

In a controlled trial organized by jacobs and Beck, 383 patients with a first acute demyelinating event (optic neuritis, transverse myeltis, or a brainstem syndrome), and two or more clinically silent lesions on brain MRI, were treated with IV methylprednisolone, and then randomized to receive either an interferon beta-1a injection (30 mcg IM q week) or a placebo. Patients were followed over three years, monitoring for the development of "clinically definite" multiple sclerosis (CDMS), with a second attack and/or change in neurologic disability. The cumulative probability of progression to CDMS was 35% in the interferon beta-1a group and 50% in the placebo group (rate ratio 0.56, $P = 0.002$). In other words, there was a 44% lower cumulative probability of converting to CDMS in the interferon beta-1a treated group. There was also a highly significant reduction in the volume of lesions on T2-weighted brain MRI scans, as well as fewer new and enhancing lesions, in patients receiving interferon beta-1a. Clinical and MRI benefits were seen within six months of treatment.

Scott and colleagues prospectively studied 98 newly diagnosed MS patients over an average follow-up of 37 months. Six prognostic factors were recorded: age at onset, symptoms at onset, MRI status, interval between first and second attack, attack frequency in the first two years, and completeness of recovery from initial attacks. Using these parameters, 24% of their patients had a high risk of progression (4-6 risk factors) and, in fact, went on to develop higher disability (EDSS > 3.5) within the short study period.

Noseworthy and associates provide a comprehensive review article on MS, including pathogenesis, epidemiologic features, diagnosis and clinical course, genetic factors, and treatment of relapsing and progressive forms of disease.

COMMENTARY

Studies on the natural history of MS have revealed that the majority of patients will have significant disability and evolve to a secondary progressive course. Recent insights into early MS brain pathology as revealed by novel MRI methodology (e.g., whole brain spectroscopy, magnetization transfer imaging, brain atrophy measures) also define an early and relentless disease process that is often subclinical. Other subtle global brain dysfunction with early cognitive impairment is difficult for the clinician to measure in the average office setting. Given this body of information, a label of "benign" MS applied to a patient at diagnosis is probably falsely reassuring, to both the patient and clinician.

Jacobs and colleagues selected a group of patients with their first demyelinating event who, on the basis of their MRI scans (≥ 2 lesions), were more likely than not to go on to CDMS. This early disease intervention study confirmed the ability of interferon beta-1a to forestall subsequent attacks and stabilize disease activity on brain MRI. This study bolsters the recommendation of the National MS Society that clinicians consider initiating therapy after a definite diagnosis of relapsing-remitting MS. However, one could argue to start immediately at the "first" attack, especially in patients with poor prognostic factors. **—brian r. apatoff**

Early Treatment of Herpes Zoster Stops Its Facial Palsy

ABSTRACT & COMMENTARY

Source: Furuta Y, et al. Early diagnosis of zoster sine herpete and antiviral therapy for the treatment of facial palsy. *Neurology* 2000;55:708-710.

Furuta and colleagues treated 163 patients older than 10 years of age with acute peripheral facial palsy (APFP), all at first called Bell's palsy, and within five days of onset.

All patients had saliva tested by polymerase chain reaction (PCR) for possible H. zoster, 82 of whom obtained results within two days. Additionaly, saliva samples were collected on all patients at 4-12 visits and had Eliza kit analysis testing for anti-varicella zoster virus (VSV) antibodies. All patients were evaluated within five days of facial weakness and those with facial palsy grade V and VI received 60 mg prednisone for four days, then tapered off. Patients positive for VZV DNA (18 = 21% of 86) were treated with acyclovir-

prednisone (a-p). Two developed zoster lesions within two days of the palsy and 13 more received a-p within seven days of onset. Three other patients received a-p eight days or later after onset. All 13 a-p patients who were treated with the drugs on or before day 8 recovered completely by three months. In contrast, the remaining 20 who received steroids alone recovered only 65% of normal facial movements by six months.

COMMENTARY

Furuta et al indicated that the time and labor required to identify the zoster testing of these patients within 2-3 days of diagnosis would limit this protocol for general use. However, many hospitals and clinical laboratories now have instruments to process PCR promptly and are only moderately expensive. On the other hand, the PDR description of undesirable reactions to acyclovir are few. Mild nausea, mild confusion among the elderly, and no adversity to breast feeding are noted. Given the distress of prolonged facial palsy and possible zoster pain, *Neurology Alert* urges treatment with prednisone 60 mg per day and acyclovir of "Bell's Palsy" within six days of onset. **—fred plum**

CME Questions

24. Autonomic nervous tissue antibodies:

a. play a significant role in the pathogenesis of idiopathic autonomic neuropathy.
b. play a significant role in the pathogenesis of pure autonomic failure
c. play a significant role in the pathogenesis of cardiac dysautonomia in type 2 diabetes.
d play a significant role in the pathogenesis of idiopathic gastrointestinal dysmotility.
e. None of the above

25. Which one of the following statements is *false*?

a. Cardiac headaches are non specific in location.
b. Cardiac headaches are not always exercise-induced.
c. Cardiac headaches are a symptom of angina pectoris.
d. Cardiac headaches are often relieved by nitrates.
e. Cardiac headaches are always occipital in location.

26. A reduction in stroke incidence has been associated with all of the following *except*:

a. increased serum levels of vitamin C.
b. dietary intake of vitamin E.
c. control of blood pressure.
d. vitamin supplementation with beta-carotene.

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10. Owner *(Do not leave blank. If the publication is owned by a corporation, give the name and address of the corporation immediately followed by the names and addresses of all stockholders owning or holding 1 percent or more of the total amount of stock. If not owned by a corporation, give the names and addresses of the individual owners. If owned by a partnership or other unincorporated firm, give its name and address as well as those of each individual. If the publication is published by a nonprofit organization, give its name and address.)*

Full Name	Complete Mailing Address
American Health Consultants	3525 Piedmont Road, Bldg. 6, Ste 400
	Atlanta, GA 30305

11. Known Bondholders, Mortgagees, and Other Security Holders Owning or Holding 1 Percent or More of Total Amount of Bonds, Mortgages, or Other Securities. If none, check box → ☐ None

Full Name	Complete Mailing Address
Medical Economics Data, Inc.	Five Paragon Drive
	Montvale, NJ 07645

12. Tax Status *(For completion by nonprofit organizations authorized to mail at nonprofit rates.) (Check one)*
The purpose, function, and nonprofit status of this organization and the exempt status for federal income tax purposes:
☐ Has Not Changed During Preceding 12 Months
☐ Has Changed During Preceding 12 Months *(Publisher must submit explanation of change with this statement)*

PS Form **3526**, September 1998 *See instructions on Reverse)*

13. Publication Name: Neurology Alert
14. Issue Date for Circulation Data Below: November 2000

15. Extent and Nature of Circulation			Average No. of Copies Each Issue During Preceding 12 Months	Actual No. Copies of Single Issue Published Nearest to Filing Date
a. Total No. Copies *(Net Press Run)*			2529	2369
b. Paid and/or Requested Circulation	(1)	Paid/Requested Outside-County Mail Subscriptions Stated on Form 3541. *(Include advertiser's proof and exchange copies)*	2268	2169
	(2)	Paid In-County Subscriptions *(Include advertiser's proof and exchange copies)*	0	0
	(3)	Sales Through Dealers and Carriers, Street Vendors, Counter Sales, and Other Non-USPS Paid Distribution	0	0
	(4)	Other Classes Mailed Through the USPS	0	0
c. Total Paid and/or Requested Circulation *(Sum of 15b(1) and 15b(2)*			2268	2169
d. Free Distribution by Mail *(Samples, Complimentary and Other Free)*	(1)	Outside-County as Stated on Form 3541	0	0
	(2)	In-County as Stated on Form 3541	0	0
	(3)	Other Classes Mailed Through the USPS	0	0
e. Free Distribution Outside the Mail *(Carriers or Other Means)*			16	16
f. Total Free Distribution *(Sum of 15d and 15e)*			16	16
g. Total Distribution *(Sum of 15c and 15f)*			2284	2185
h. Copies Not Distributed			245	184
i. Total *(Sum of 15g. and h.*			2529	2369
Percent Paid and/or Requested Circulation *(15c divided by 15g times 100)*			99	99

16. Publication of Statement of Ownership
Publication required. Will be printed in the November issue of this publication. ☐ Publication not required.

17. Signature and Title of Editor, Publisher, Business Manager, or Owner: Publisher — Date: 10/18/00

I certify that all information furnished on this form is true and complete. I understand that anyone who furnishes false or misleading information on this form or who omits material or information requested on the form may be subject to criminal sanctions (including fines and imprisonment) and/or civil sanctions (including multiple damages and civil penalties).

Instructions to Publishers

1. Complete and file one copy of this form with your postmaster annually on or before October 1. Keep a copy of the completed form for your records.
2. In cases where the stockholder or security holder is a trustee, include in items 10 and 11 the name of the person or corporation for whom the trustee is acting. Also include the names and addresses of individuals who are stockholders who own or hold 1 percent or more of the total amount of bonds, mortgages, or other securities of the publishing corporation. In item 11, if none, check the box. Use blank sheets if more space is required.
3. Be sure to furnish all circulation information called for in item 15. Free circulation must be shown in items 15d, e, and f.
4. Item 15h., Copies not Distributed, must include (1) newsstand copies originally stated on Form 3541, and returned to the publisher, (2) estimated returns from news agents, and (3), copies for office use, leftovers, spoiled, and all other copies not distributed.
5. If the publication had Periodicals authorization as a general or requester publication, this Statement of Ownership, Management, and Circulation must be published; it must be printed in any issue in October or if the publication is not published during October, the first issue printed after October.
5. In item 16, indicate date of the issue in which this Statement of Ownership will be published.
6. Item 17 must be signed.

Failure to file or publish a statement of ownership may lead to suspension of second-class authorization.

PS Form **3526**, September 1999 *(Reverse)*

In Future Issues:

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