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INSIDE

Financial Disclosure:

Neurology Alert's physician editor, Matthew Fink, MD, reports no consultant, stockholder, speaker's bureau, research, or other relationships related to this field of study.
Peer reviewer M. Flint Beal, MD, reports no consultant, stockholder, speaker's bureau, research, or other financial relationship with any company having ties to this field of study.

What Works for Bell's Palsy?

ABSTRACT & COMMENTARY

By Michael Rubin, MD

Professor of Clinical Neurology, Weill Medical College of Cornell University, NewYork-Presbyterian Hospital

Dr. Rubin is on the speaker's bureau for Athena Diagnostics, and does research for Pfizer and Merck.

Synopsis: *Prednisone treatment, with or without an antiviral drug, improves Bell's palsy outcome.*

Source: Sullivan FM, et al. Early treatment with prednisolone or acyclovir in Bell's palsy. *N Engl J Med* 2007;357:1598-1607; Gilden DH, Tyler KL. Bell's palsy — is glucocorticoid treatment enough? *N Engl J Med* 2007;357:1653-1655.

ARE STEROIDS, ACYCLOVIR, OR SURGICAL FACIAL NERVE DECOMPRESsion effective for Bell's palsy? According to an American Academy of Neurology Practice Parameter,[1] benefit from these therapies "has not been definitively established", although evidence suggests "that steroids are probably effective, acyclovir combined with prednisone is possibly effective", and insufficient evidence was available regarding facial nerve decompression to make a recommendation. Well-designed studies were warranted. We now have the results of one such study addressing treatment with prednisolone and acyclovir.

Commissioned by the Health Technology Assessment Program of the National Institute for Health Research in Scotland to determine if prednisolone and/or acyclovir enhances recovery from Bell's palsy when used early in the course of disease, 17 Scottish centers conducted a randomized, double-blind, placebo-controlled, factorial trial. They enrolled 551 patients between June 2004 to June 2006 who had recent (72 hours) onset of Bell's palsy. Adults age 16 and older who had unilateral idiopathic facial weakness were divided into four groups and treated for 10 days with either: 1) prednisolone (50 mg qd), 2) acyclovir (2000 mg qd), 3) prednisolone and acyclovir, or 4) placebo. Exclusionary criteria included multiple sclerosis, pregnancy, uncontrolled diabetes, herpes zoster, sarcoidosis, breast-feeding, and systemic infection. Follow-up assessment occurred at three and nine months using a questionnaire and digital camera. Facial nerve function as graded by the House-Brackman system was the primary outcome measure; it was assessed by photographs in four poses: at rest,

VOLUME 26 • NUMBER 4 • DECEMBER 2007 • PAGES 25-32

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with forced smile, bared teeth, and buried eyelashes. Secondary outcome measures included health-related quality of life measured with Health Utilities Index Mark 3, facial appearance using the Derriford Appearance scale 59, and pain measured by the Brief Pain Inventory. Statistical analyses comprised the two-sided Fisher's exact test, t-tests, Mann-Whitney tests, and Wald tests, with $p<0.05$ considered statistically significant.

At three months, recovery rates were 83% versus 63.6%, respectively, for prednisolone versus non-prednisolone treated patients, and 71.2% versus 75.7%, respectively, for acyclovir versus non-acyclovir treated patients. At nine months, recovery rates increased to 94.4% versus 81.6% ($p<0.001$), respectively, for prednisolone versus non-prednisolone treated patients, and 85.4% versus 90.8% ($p=0.10$, non-significant), respectively, for acyclovir versus non-acyclovir treated patients. No significant additional benefit was accrued in the combined prednisolone and acyclovir treated patients, of whom 79.7% and 92.7%, respectively, improved at three and nine months. Adverse effects were not serious in any group. Treatment of Bell's palsy with prednisolone, within 72 hours of onset, significantly improves the likelihood of complete recovery at three and nine months. No benefit is accrued by using acyclovir, either alone or in combination with prednisolone.

COMMENTARY

As noted in the accompanying editorial, unlike acyclovir, other antiviral agents may yet be beneficial when added to prednisone. Based on a multicenter, randomized, placebo-controlled trial, valacyclovir plus prednisone appeared to improve outcome compared to prednisone alone.[2] Astonishingly, investigators in this study, who administered treatment and assessed outcome, were not blinded as to group assignment. In a randomized, controlled, prospective trial recently reported online, prednisone was compared to combined prednisone and famciclovir.[3] Treatment was begun within one week of onset. Outcome measures, including clinical appearance, viral antibody titers, and electromyographic changes, were significantly improved in the combined therapy group compared to prednisone alone. Acyclovir is now the inglorious past for Bell's palsy, but the future remains bright for other anti-viral agents. Until further studies show otherwise, patients with Bell's palsy should receive a 10-day course of prednisone combined with valacyclovir or famciclovir. ■

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Neurology Alert, ISSN 0741-4234, is published monthly by AHC Media LLC, 3525 Piedmont Road., NE, Building. 6, Suite 400, Atlanta, GA 30305.

SENIOR VICE PRESIDENT/ GROUP PUBLISHER : Brenda Mooney.
ASSOCIATE PUBLISHER: Lee Landenberger.
SENIOR MANAGING EDITOR: Suzanne Thatcher
GST Registration Number: R128870672.
Periodicals postage paid at Atlanta, GA.
POSTMASTER: Send address changes to *Neurology Alert*, P.O. Box 740059, Atlanta, GA 30374.

Back issues: $42. Missing issues will be fulfilled by Customer Service free of charge when contacted within one month of the missing issue's date.

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Lupus and the Nervous System

ABSTRACT & COMMENTARY

By Joseph E. Safdieh, MD

Assistant Professor of Neurology, Weill Medical College, Cornell University

Dr. Safdieh reports no financial relationships relevant to this field of study.

Synopsis: *Lupus can involve the nervous system in many ways and sometimes present with neuropsychiatric symptoms. Clinicians should consider the diagnosis of lupus in patients with unexplained neuropsychiatric symptoms.*

Source: Joseph FG, et al. CNS lupus: a study of 41 patients. *Neurology* 2007;69:644-654.

SYSTEMIC LUPUS ERYTHEMATOSUS IS ONE OF A LARGE number of rheumatological conditions with neuropsychiatric manifestations. In fact, the American College of Rheumatology criteria for the diagnosis of lupus include neurological manifestations as one of 11 diagnostic features. The neuropsychiatric manifestations are protean; they include a large number of symptoms and signs, many of which are nonspecific in nature. These have traditionally included seizures, spinal cord dysfunction, psychosis, stroke, abnormal movements (chorea),

and peripheral nervous system dysfunction. The authors of this study retrospectively identified patients with nervous system manifestations of lupus in an effort to better understand the natural history of this disease.

Joseph et al identified a total of 41 patients who satisfied the criteria for CNS lupus; 38 of these patients were female. The mean age for the first neuropsychiatric presentation was 41 years and the mean latency from diagnosis of lupus to presentation of neuropsychiatric symptoms was 5.75 years. The most commonly reported neuropsychiatric features included: headaches (54%), seizures (42%), visual disturbances (32%), fatigue (27%), hemiparesis (24%), memory impairment (24%), and confusion (24%). Arterial stroke was seen in 17% of patients. No cases of venous sinus thrombosis were identified in this series. Two of the patients with stroke had elevated antiphospholipid antibodies. Two patients developed myelopathy.

Of note, in 24% of these patients, neuropsychiatric manifestations were the initial presenting feature of lupus. The erythrocyte sedimentation rate (ESR) was elevated in the majority of these cases, but a normal ESR did not exclude CNS lupus. Neuropsychiatric manifestations in these patients were varied and included movement disorders, seizures, and meningeal involvement, among others. Symptoms included features not traditionally associated with lupus, including parkinsonism. The authors highlighted a case of a 74-year-old woman with levodopa-unresponsive parkinsonism who improved on hydroxychloroquine and prednisolone. This patient demonstrated other abnormalities on neurological examination, and also had an elevated ESR and positive ANA (anti-nuclear antibodies) with low complement levels.

The spinal fluid was abnormal in 39% of cases in which it was analyzed. Abnormalities included elevated protein, mild lymphocytic pleocytosis, and the presence of oligoclonal bands. The presence of abnormal CSF correlated with worse prognosis of CNS lupus. MRI imaging was abnormal in 64% of patients. These abnormalities included nonspecific white matter hyperintensities, infarcts, and in one case each, optic nerve enhancement and leptomeningeal enhancement. EEG was abnormal in 79% of patients, with the majority of patients demonstrating nonspecific slowing.

At the end of the study period, the majority of the patients demonstrated minor or moderate disability. Five patients were asymptomatic and five patients died. The majority of patients suffered repeat attacks and most patients received treatment with steroids, with or without other immunosuppressive agents.

COMMENTARY

This study demonstrates a number of important points. Primary neurological presentation of lupus is not rare, and the diagnosis should be considered in patients with unexplained neurological symptoms, especially those in the typical demographic group. Chorea, traditionally considered a common movement disorder in lupus, was less common than parkinsonism and myoclonus in this cohort of patients. Patients with primary neurological lupus can have a normal ESR. Abnormal CSF analysis correlates with a poorer prognosis. Seizures in lupus patients are common. In this cohort, the incidence is even higher than previously observed; however, this partly may be explained by case-ascertainment bias.

This is an important study for neurologists as well as internists and rheumatologists. Neurologists and psychiatrists should remember to keep lupus in the differential diagnosis of otherwise unexplained neuropsychiatric symptoms. Internists and rheumatologists caring for patients with lupus should carefully screen these patients for the development of neuropsychiatric manifestations, and adjust anti-inflammatory therapy accordingly as serious disability can result in some cases.

Role of Prophylactic Whole Brain Radiotherapy for Small-Cell Lung Cancer

ABSTRACT & COMMENTARY

By Adília Hormigo, MD, PhD

Assistant Professor of Neurology, Weill Medical College, Cornell University

Dr. Hormigo reports no financial relationships relevant to this field of study.

Synopsis: *In this study of patients with extensive small-cell lung cancer, prophylactic brain irradiation decreased the incidence of symptomatic brain metastases and prolonged disease-free survival and overall survival without significant impact on global health status.*

Source: Slotman B, et al. Prophylactic cranial irradiation in extensive small-cell lung cancer. *N Engl J Med* 2007;357:664-672.

It is well established that prophylactic whole brain radiotherapy plays a role in decreasing the incidence of brain metastases in patients with limited small-cell lung cancer.[1] A multicenter study was conducted in Europe to evaluate the role of prophylactic cranial radiation in patients ages 18-75 who responded to chemotherapy for extensive small-cell lung cancer, which was defined as disease beyond the hemithorax and supraclavicular nodes

or presence of a malignant pleural effusion. After a response was obtained to 4-6 cycles of chemotherapy, patients who had no evidence of brain or leptomeningeal disease by contrast head CT scan or MRI were randomized to receive prophylactic 25-39 Gy of cranial irradiation or no further treatment. The primary end-point was development of symptomatic brain metastases, defined by a symptom suggestive of CNS disease and a positive contrast head CT scan or MRI. Each group accrued 143 patients. The risk for symptomatic metastases was significantly lower in the group that received irradiation (hazard ratio, 0.27; $p<0.001$). The cumulative risk of brain metastases within one-year was 14.6% in the irradiated group versus 40.4% in the control group. A significant increase in median disease-free survival from 12 to 14.7 weeks ($p=0.02$) and median overall survival from 5.4 to 6.7 months ($p=0.003$) after randomization was seen for the irradiated group vs. the control group. The one-year survival rate was 27.1% in the irradiated group versus 13.3% in the control group.

The authors concluded that in patients with extensive small-cell lung cancer, prophylactic brain irradiation decreased the incidence of symptomatic brain metastases and prolonged disease-free survival and overall survival without significant impact on global health status.

COMMENTARY

This multi-center trial conducted in Europe compared prophylactic cranial radiotherapy to no further treatment in patients with extensive small-cell lung cancer and found a significant benefit for the patients who received cranial irradiation. The treatment was well tolerated and there were no significant side effects. The allowed use of head CT scan instead of MRI for follow-up in some patients is a limitation of the study. The optimal schedule of radiotherapy remains to be determined as several schedules were used. Nevertheless, the study clearly concluded that prophylactic radiotherapy should be used for patients with extensive small-cell lung cancer after chemotherapy is completed and a response is obtained to the initial chemotherapy treatment. While global health was not different between the two groups, the late neurocognitive consequences of prophylactic whole brain radiation were not assessed and remain a potential concern as better treatments improve the length of survival. However, prophylactic radiotherapy should be extended to include these patients in addition to the standard recommendation for patients with limited small-cell lung cancer who have a complete response after chemotherapy.

Reference

1. Aupérin A, et al. *N Engl J Med* 1999;341:476-484.

Can ADEM Be Distinguished from MS During an Acute Episode of Fulminant Demyelination of the CNS?

ABSTRACT & COMMENTARY

By Susan Gauthier, DO, MPH

Assistant Professor of Neurology, Weill Medical College of Cornell University

Dr. Gauthier reports no financial relationships relevant to this field of study.

Synopsis: *In adults presenting with an acute episode of fulminant demyelination of the central nervous system (CNS), atypical symptoms for multiple sclerosis (MS), gray matter involvement on MRI, and absence of oligoclonal bands in the cerebrospinal fluid (CSF) can distinguish acute disseminated encephalomyelitis (ADEM) from MS.*

Source: de Seze J, et al. Acute fulminant demyelinating disease: a descriptive study of 60 patients. *Arch Neurol* 2007;64:1426-1432.

ADEM IS A FULMINANT DEMYELINATING EPISODE occurring within the central nervous system and is typically monophasic, following an infectious event or vaccination. ADEM has been studied more often in pediatric cohorts due to its higher incidence in children and young adolescents; therefore, information regarding the clinical and MRI manifestations, as well as the rate of conversion to MS in adults, is scant or lacking. The ability to distinguish MS from ADEM would be advantageous given the proven benefit of early treatment of MS.

In this large multi-center, retrospective study, de Seze et al identified 60 adult patients (older than age 16) as having a diagnosis of ADEM within a European MS database. Alterations in consciousness, hypersomnia, aphasia, hemiplegia, paraplegia, seizure, vomiting, bilateral optic neuritis, or confusion were considered atypical for MS. Six patients were categorized as having multiphasic demyelinating encephalomyelitis (MDEM) due to recurrence of initial symptoms; these patients were not included in the analysis. Thirty-five patients were categorized as having ADEM (monophasic neurologic symptoms), and 19 patients were labeled as having MS based upon the addition of a new clinical symptom least one month after the first episode.

There was a 32% conversion rate to clinically definite MS after a mean of 37 months. MS patients were found to be younger at presentation (27 years versus 36 years,

p=0.04), and although prior infections or vaccinations were more common in ADEM compared to MS, the difference was not significant. Patients with ADEM more often had atypical symptoms, although no one symptom was significant for this association. Corpus callosum lesions were more common in MS patients (p<0.001), whereas gray matter lesions (basal ganglia or cortical) were more common in ADEM patients (p<0.001). The numbers of total T2 lesions, periventricular lesions, spinal cord lesions, or gadolinium-enhanced lesions were not significantly different between the two groups. Three patients with ADEM had new gadolinium-enhanced lesions as compared to nine MS patients (p<0.001). Similarly, 11 patients with MS had new T2 hyperintense lesions as compared to only one ADEM patient (p<0.001). Oligoclonal bands more often were found in the CSF of MS patients (84% versus 20%, p<0.001); however, no differences were found in CSF total white blood count (>30/microliter) or protein level (>1g/dL). Based upon the results, a new criterion was proposed to differentiate MS from ADEM. ADEM diagnosis required two of three of the following features: one or more atypical symptoms, absence of oligoclonal bands in the CSF, or gray matter involvement (basal ganglia or cortical lesions). The sensitivity was calculated to be 82.9%, specificity to be 94.7%, and positive predictive value to be 96.7%.

COMMENTARY

The distinction between MS and ADEM has never been fully described or understood and remains a diagnostic dilemma. This study represents one of the largest descriptive series of adult-onset ADEM, and it identified a set of distinguishing characteristics for ADEM compared to MS. Furthermore, as demonstrated in this study, differences exist between adult-onset and pediatric-onset ADEM. Adult-onset ADEM had a higher conversion rate to MS as compared to pediatric-onset disease, which ranges between 9% and 35%,[1] and a less direct association with vaccinations or prior infection. In addition, adult-onset ADEM had a similar number of periventricular lesions as compared to MS, a finding that differs from the pediatric cohort studies.[1]

Study limitations are unavoidable because of the overlap between ADEM and MS. Specific limitations of this study include the unexplained exclusion of patients with MDEM and the one-month interval to define MS, given that previous work in ADEM had recommended a two-month interval to accurately define MS.[1] A small percentage of patients with ADEM have MRI progression, but the significance of this observation in relation to the development of MS has yet to be established. Finally, the predictive potential of the proposed criteria will need to be evaluated in a separate cohort to ensure reliability. Despite these limitations, this study highlights clinical features that might help to identify patients with a clinical presentation of ADEM who could be at risk for developing MS and would benefit from early intervention with immunomodulatory therapy. ■

Reference

1. Menge T, et al. *Arch Neurol* 2005;62:1673-1680.

PET Imaging May Accurately Diagnose Cerebral Amyloid Angiopathy (CAA)

ABSTRACT & COMMENTARY

By Alan Z. Segal, MD

Associate Professor, Department of Neurology, Weill-Cornell Medical College, Attending Neurologist, NewYork-Presbyterian Hospital

Dr. Segal is on the speaker's bureau for Boehringer Ingelheim.

Synopsis: *PET imaging with Pittsburgh Compound B is a promising new technique to non-invasively diagnose CAA.*

Source: Johnson KA, et al. Imaging of amyloid burden and distribution in cerebral amyloid angiopathy. *Ann Neurol* 2007;62:229-234.

THE DIAGNOSIS OF CEREBRAL AMYLOID ANGIOPATHY (CAA) is made definitively on the basis of pathological examination of brain tissue. CAA also may be diagnosed indirectly based on multiple microhemorrhages on gradient echo MRI. The thioflavin derivative known as Pittsburgh Compound B (Pi-B) is known to bind to amyloid on PET imaging and has been used, as an investigational tool, in studies of Alzheimer's disease. Pi-B PET imaging also may be a useful method of diagnosing CAA in living subjects.

The authors studied six non-demented subjects with probable CAA, 15 healthy control subjects, and nine patients with probable Alzheimer's disease. PiB uptake was increased in CAA compared to healthy subjects, but was less than that seen in Alzheimer's patients. Importantly, CAA patients differed from Alzheimer's patients in showing an occipital predilection for Pi-B uptake, with a significantly increased occipital to global ratio. As the authors observe, this occipital predominance, known to occur in the pathology of CAA, may help tease out vascular as opposed to plaque amyloid burden.

COMMENTARY

This study has important clinical implications since CAA may pose a major risk for intracerebral hemorrhage in elderly patients requiring warfarin therapy for atrial fibrillation and other indications. Pi-B PET imaging may potentially diagnose CAA non-invasively in patients with isolated hemorrhage or even among patients who have never had an intracerebral hemorrhage. Validation in a larger study is warranted, and pathologic confirmation will be important. ■

New Genetic Risk Factors for MS Identified: More Targets for Immune Therapy

SPECIAL REPORT

By Brian R. Apatoff, MD, PhD
Director, Multiple Sclerosis Clinical Care and Research Center, Department of Neurology and Neuroscience, NewYork-Presbyterian Hospital, Cornell Campus
Dr. Apatoff reports no financial relationship relevant to this field of study.

Synopsis: *Whole genome scans identified two new genetic variations associated with multiple sclerosis (MS) that may provide sites of immune intervention.*

Sources: International Multiple Sclerosis Genetics Consortium. Risk alleles for multiple sclerosis identified by a genomewide study. *N Engl J Med* 2007;357:851-862; Gregory SG, et al. Interleukin 7 receptor alpha-chain (IL7R) shows allelic and functional association with multiple sclerosis. *Nat Genet* 2007;39:1083-1091; Lundmark F, et al. Variation in interleukin 7 receptor alpha chain (IL7R) influences risk of multiple sclerosis. *Nat Genet* 2007;39:1108-1113; Peltonen L. Editorial. Old suspects found guilty — the first genome profile of multiple sclerosis. *N Engl J Med* 2007;357:927-929; Rose JW, et al. Daclizumab phase II in relapsing and remitting multiple sclerosis: MRI and clinical results. *Neurology* 2007;69:785-789.

USING NEW DNA CHIP TECHNOLOGIES, THE ABOVE investigators were able to screen the whole genome of many thousands of subjects, testing more than 300,000 genetic locations for single-nucleotide polymorphisms (SNPs), variations more commonly seen in MS compared to those without the disease. These data reconfirmed the strong association of the HLA-DR locus in MS. Additional alleles were identified in the interleukin-2 receptor (*IL2RA*) gene and the interleukin-7 receptor (*IL7R*) gene. The *IL2RA* gene also has been associated with diabetes and Graves disease.

In an accompanying editorial, however, Peltonen provides perspective on the relative significance of these novel genetic markers and their association with MS. For example, the SNP genetic variants associated with MS for *IL2RA* and *IL7RA* also are quite common in the general population (up to 70%), and contribute only a very minor increased risk for disease. Thus, the relative risk of MS from the *IL2RA* and *IL7RA* SNPs is quite small, compared to the previously identified HLA region that confers the major genetic risk of MS.

The *IL7R* is critical for the regulation of the regulatory T-cell pool. Similarly, the *IL2R* is important in the regulation of T-cell responses, and a humanized monoclonal antibody against the *IL2R*, daclizumab (anti-CD25), is already FDA-approved for treatment of renal allograft rejection.

In a recent phase II clinical trial, Rose and colleagues studied nine patients with relapsing-remitting MS on beta-interferon (beta-IFN) therapy with break-through relapses and continued enhancing lesions on brain MRI. Patients were treated with daclizumab (1 mg/kg IV) every two weeks for the first two doses, and then monthly for 27.5 months. At 5.5 months, beta-IFN was discontinued. Patients were monitored with monthly MRI scans and clinical rating scales. In three of the nine patients in whom continued brain MRI activity was noted, the daclizumab dosing was increased (1.5 mg/kg IV) and beta-IFN was restarted. Overall, there were significant reductions in contrast enhancing lesions and clinical relapses in the daclizumab treated patients compared to their baseline disease activity. The effectiveness of this anti-IL-2 receptor monoclonal antibody supports its role in MS disease pathogenesis. The relative safety and benefits of this selective immune intervention, especially compared to other monoclonal therapies such as natalizumab and rituximab, remains to be defined in a larger phase III trial. ■

Essential Tremor: Not So Benign?

ABSTRACT & COMMENTARY

By Claire Henchcliffe, MD, DPhil
Assistant Professor, Department of Neurology, Weill Medical College, Cornell University
Dr. Henchcliffe reports no financial relationship to this field of study.

Synopsis: *In a population-based study of the elderly in central Spain, individuals with essential tremor beginning after age 65 had a two-fold increased likelihood of*

incident dementia when compared with controls without essential tremor.

Source: Bermejo-Pareja F, et al. Risk of incident dementia in essential tremor: a population-based study. *Mov Disord* 2007;22:1573-1580.

THE NEDICES (NEUROLOGICAL DISORDERS IN CENTRAL Spain) survey is a population-based study of age-associated conditions affecting individuals age 65 and older in three communities in central Spain. Baseline evaluations, including a screening question for essential tremor (ET), were completed from 1994 to 1995; those with baseline dementia (based upon Diagnostic and Statistical Manual of Mental Disorders [DSM]-IV criteria) were excluded. ET was diagnosed in 206/3891 individuals (204 by direct examination). Those with ET were older than those without (74.6 ± 6.7 versus 73.1 ± 6.3 years, p=0.003), and depressive symptoms were more commonly associated with ET (43.5% versus 25.8%, p<0.001), but there was no significant difference by gender, smoking, alcohol consumption, heart disease, hypertension, diabetes, or stroke. Follow-up occurred at a mean of 3.2 years; 16/206 (7.8%) ET cases had developed dementia, compared with 145/3685 (3.9%) controls. Dementia followed ET diagnosis by a mean time period of 10.5 years (range, 2.5-53 years). Ninety-seven ET cases had a younger onset, with tremor beginning before they were age 65. Of these, only two (2.1%) developed dementia, compared with 14/109 (12.8%) older-onset ET cases (p=0.004). Adjusted Cox models were applied to account for differences between groups in age and educational level, or age, educational level, alcohol, stroke, hypertension, and depression. Relative risk (RR) for dementia was 1.84-1.98 (depending on adjustments applied, p=0.01-0.04) in older onset ET versus controls. In younger-onset ET, adjusted RR did not reach significance. Possible or probable Alzheimer's disease (AD) accounted for the majority of incident dementia (71.4%), and older-onset ET was associated with an adjusted RR for AD incidence of 2.04-2.13.

COMMENTARY

Cognitive deficits have been reported in association with ET. While these are usually mild, and can include memory or frontal executive function, they have been little-studied to date and their true impact and significance is unclear. The authors have previously demonstrated the association of ET with prevalent dementia, and this community-based study using the same NEDICES database extends those findings. As they acknowledge, despite careful record review and direct examination in the majority of ET cases, their study design has a number of inherent problems. This includes the presence of confounding factors that are difficult to adjust for, the (low) likelihood of misdiagnosis, and the possibility of patients developing an unrelated neurodegenerative process. A small proportion of ET patients have been reported to develop Parkinson's disease; therefore, could synuclein pathology be a contributing factor to development of dementia in the older-onset ET cases? Extrapolating from independent studies, the number of individuals expected to develop Parkinson's disease in this time period would simply not account for the increased dementia risk observed. As a result, an alternative explanation needs to be examined. It is becoming evident that the true spectrum of ET likely involves features other than tremor, such as ataxia, and the present study underscores likely involvement of regions outside of the cerebellum in at least a subset of cases. The association of ET with dementia, particularly given its potential impact on quality of life, will require further study. We need to determine who is at risk to provide adequate counseling and treatment for our ET patients. ■

Deep Brain Stimulation for Primary Torsion Dystonia

ABSTRACT & COMMENTARY

By Panida Piboolnurak, MD

Assistant Professor, Department of Neurology and Neuroscience, Weill Medical College, Cornell University

Dr. Piboolnurak reports no financial relationship relevant to this field of study.

Synopsis: *Deep brain stimulation of the internal globus pallidus at 60 Hz is effective treatment for primary dystonia.*

Source: Alterman RL, et al. Sixty hertz pallidal deep brain stimulation for primary torsion dystonia. *Neurology.* 2007;69: 681-688.

DEEP BRAIN STIMULATION (DBS) OF THE GLOBUS PALlidus interna (GPi) is an effective therapy for primary dystonia. In most case series, high frequencies (130-185 Hz) and wide pulse width (120-450 mcsec) were used based on the experience in Parkinson's disease and essential tremor. This can result in excessive battery consumption and may cause muscle contractions because of current spreading to the adjacent internal capsule.

Alterman and colleagues reported their experience in using 60 Hz stimulation in 15 consecutive patients with primary dystonia (12 men and 3 women). Twelve had

DYT1 gene mutation (9 men and 3 women). Median age at the time of surgery was 20 years, with a median symptom duration of six years. The electrodes were placed in posteroventral GPi (bilateral in 13 patients and unilateral in 2 patients). The stimulation was set at 60 Hz in all patients. The stimulating contacts were selected from four available contacts (0-3) on each side based on the clinical response and tolerability. The initial voltage and pulse width were set at 2.5 volts and 120 mcsec based on their experience. Voltage or pulse width was then adjusted monthly or bimonthly to maximize the benefit or to reduce adverse effects. Frequency was kept constant at 60 Hz.

The motor subscales of Burke-Fahn-Marsden Dystonia Rating Scale (BFMDRS-M) and disability subscales (BFMDRS-D) were employed for clinical assessment in an open-label fashion at baseline (within 1 week of surgery), and at 1, 3, 6, and 12 months after the initial programming. At the baseline, the median BFMDRS-M and BFMDRS-D scores were 35 and 8, respectively. Median improvement in BFMDRS-M was 38%, 76%, 82%, and 89% at 1, 3, 6, and 12 months, respectively. Median improvement in BFMDRS-D was 25%, 64%, 70%, and 75% at 1, 3, 6, and 12 months, respectively.

The outcome correlated with age at the time of surgery (better in patients younger than 21) and the duration of symptoms, but did not correlate with *DYT1* status, age at disease onset, disease severity, or gender. There were no differences in the outcome at one year between patients with phasic and tonic dystonia. However, patients with phasic dystonia had a trend toward better improvement at one month. Of 13 patients who were taking medications for dystonia preoperatively, 7 were able to stop medications at their last follow-up (12-30 months). Six patients were able to reduce medications by at least 50%. The intrathecal baclofen pump required by one patient could be removed.

Of 28 electrodes, 27 were unipolar stimulation (11 with single monopolar, 14 with double contiguous monopolar, and 2 with triple monopolar) with a mean amplitude of 3.0 ± 0.3 volts. The most common contact used was contact 1 (37%), followed by contacts 2, 0, and 3. Pulse widths at the last follow-up ranged from 120 to 270 mcsec. The average battery consumption was 55 microAmp, which was approximately half of what was observed in stimulation with higher frequency according to the authors' unpublished observations.

COMMENTARY

GPi DBS is an effective treatment for primary dystonia. However, there was no established guideline for the electrical parameter setting in dystonia. Based on experience with Parkinson's disease, high frequency stimulation has been used. Wide pulse width also tends to be used due to a belief that a wide pulse width is required to cover the larger dimensions of GPi compared to the subthalamic nucleus. Combination of high frequency and high pulse width will shorten the battery life and can cause muscle contractions due to electrical current spreading to the adjacent internal capsule. This study provided the evidence that lower frequency (60 Hz) can be effective in dystonia. Although the pulse width used in this study is not in the highest end, it is still in the higher range. Without a direct comparison with higher frequency settings, it is difficult to know whether higher frequency could be more effective than 60 Hz stimulation. Future studies with direct comparison among different pulse widths and frequencies will be required to provide a guideline for the best parameter setting. ■

CME Questions

18. Optimum treatment for Bell's palsy, within 72 hours of onset, is:
a. Prednisone alone
b. Acyclovir alone
c. Prednisone and acyclovir
d. Prednisone and valacyclovir
e. Any or none of the above

19. What is the most common neurological symptom in patients with lupus?
a. Ataxia
b. Chorea
c. Headache
d. Seizures
e. Visual disturbances

20. Which of the following is true for small-cell lung cancer patients with no evidence of brain metastases?
a. Prophylactic cranial radiotherapy should only be given for patients with limited small-cell lung cancer.
b. Prophylactic cranial radiotherapy should only be given for patients with extensive small-cell lung cancer.
c. Prophylactic cranial radiotherapy does not prolong overall survival in patients with extensive small-cell lung cancer.
d. Prophylactic cranial radiotherapy increases median disease-free survival in patients with extensive small-cell lung cancer.

21. Which of the following CSF results is more likely to be found in adult-onset ADEM compared to MS?
a. Elevated protein (>1g/dL)
b. The presence of oligoclonal bands
c. Elevated total white blood cell count (>30/microliter)
d. All of the above
e. None of the above

Answers: 18. d.; 19. c; 20. d; 21. e

In Future Issues:

MRI Findings in Asymptomatic People

PHARMACOLOGY WATCH

Supplement to Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Infectious Disease Alert, Internal Medicine Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports, Travel Medicine Advisor.

Adult Immunization Guidelines from CDC Released

In this issue: *Updated Immunization Guidelines from the CDC; Do antivirals have a role in the treatment of Bell's palsy? Topiramate is a promising treatment for alcohol dependence; and FDA Actions.*

The *Annals of Internal Medicine* has published updated Adult Immunization Guidelines from the CDC as an early release article on their website dated October 18. Full guideline will be available in the November 20 print edition. The guideline has several important changes and updates.

The new herpes zoster vaccine is added to the guideline this year. The vaccine should be given routinely to all immunocompetent adults age 60 and older. It is not recommended for immunocompromised adults as it is a live attenuated virus. The vaccine is given once in a lifetime, and does not require a booster.

The new human papilloma virus has also been added. The vaccine protects against 4 types of HPV, which causes 90% of genital warts and 70% of cervical cancers. It is recommended for women aged 11 to 26 years. It requires three doses given at zero, 2 and 6 months. It should not be given to pregnant women.

The new pertussis vaccine is coupled with diphtheria and tetanus to form Tdap (Adacel- Sanofi Pasteur). This is a 1-time, 1-dose vaccine that should be given to all adults age 64 or younger when they are scheduled for their next tetanus (Td) booster. Tetanus boosters should be given every 10 years, but the interval may be shortened to as little as two years for high-risk patients including postpartum women, close contact of infants younger than 12 months of age, and all healthcare workers with direct patient contact. It has not been tested in adults age 65 or older. This vaccine is different from the previously approved Tdap for adolescents aged 10 to 19 (Boostrix-GlaxoSmithKline).

There are now 15 indications for influenza vaccine. New indications include those who have difficultly handling respiratory secretions or have increased risk of aspiration. All women who are pregnant or will be pregnant during the flu season should be vaccinated. All healthcare workers should be vaccinated unless they have strong contraindications.

Hepatitis B vaccine recommendations have changed, and the vaccine is now recommended for all sexually active adults who are not in a long-term mutually monogamous relationship.

Because of several recent large-scale mumps outbreaks in this country, a mumps vaccine booster is now recommended for specific age groups, especially adults who work in healthcare settings. The standard is to give MMR, even if immunity exists for one or more of the components of MMR.

The pneumococcal vaccine recommendations remain the same. The vaccine should be given at age 65 unless the patient has specific risk factors, in which case it should be given to those younger than 65. A small subgroup of patients should be given a second booster. If the vaccine was initi-

This supplement was written by William T. Elliott, MD, FACP, Chair, Formulary Committee, Kaiser Permanente, California Division; Assistant Clinical Professor of Medicine, University of California-San Francisco. In order to reveal any potential bias in this publication, we disclose that Dr. Elliott reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study. Questions and comments, call: (404) 262-5431. E-mail: iris.young@ahcmedia.com.

ated under age 65 for high-risk patients, a booster should be given at age 65 or five years after the initial vaccine. If the vaccine was initiated over age 65, a booster should only be given to immunocompromised patients after five years. The vaccine should not be given every five years (a common misconception). In fact, no one should receive more than two doses under any circumstances. There is even some evidence that more than two doses may be harmful and could potentially attenuate the immune response.

Antivirals and Bell's Palsy?

Do antivirals have a role in the treatment of Bell's palsy? This question has been debated for decades, with several small studies indicating a relationship between herpes simplex infections and facial paralysis. Despite this, treatment with acyclovir or valacyclovir has not been proven to be effective in treating Bell's palsy. Regardless, antivirals are frequently prescribed along with oral steroids. A new study confirms that steroids are useful, but antivirals are not. Nearly 500 patients with new onset of Bell's palsy were randomized to 10 days of treatment with prednisolone, acyclovir, both agents, or placebo. The primary outcome was recovery of facial function. At three months, the proportion to patients who had recovered facial function were 83.0% in the prednisolone group compared with 63.6% among patients who did not receive prednisolone ($P < 0.001$) and 71.2% in the acyclovir group as compared to 75.7% among patients who did not receive acyclovir (adjusted $P = 0.50$). After nine months, recovery was 94.4% for prednisolone and 81.6% for no prednisolone ($P < 0.001$) and 85.4% for acyclovir and 90.8% for no acyclovir (adjusted P = 0.10). For patients treated with both drugs, recovery was 79.7% at 3 months ($P < 0.001$) and 92.7% at nine months ($P < 0.001$). There were no serious adverse effects in either group. The authors conclude that early treatment with prednisolone significantly improves the chance of complete recovery, while there's no evidence of benefit with acyclovir alone or in combination with the steroid (*NEJM*. 2007; 357:1598-1607).

Topiramate Promising for Alcohol Treatment

Topiramate is a promising treatment for alcohol dependence according to a new study. The drug was shown to be effective in this role in a small study published in 2003. This new, larger multisite 14 week double-blind, randomized, placebo controlled trial enrolled 371 men and women age 18 to 65 years who were diagnosed with alcohol dependence. Up to 300 mg per day of topiramate was given to 183 participants while 188 were treated with placebo. Both groups were enrolled in a weekly compliance enhancement intervention program. The primary end point was self-reported percentage of heavy drinking days, while secondary outcomes included other self-reported drinking measures along with laboratory measures of alcohol consumption. Topiramate was more efficacious than placebo at reducing percentage of heavy drinking days from baseline to 14 weeks (mean difference 8.44%; 95% CI, 3.07%-13 .80%; $P = .002$). Topiramate also reduced all of the drinking outcomes ($P <.001$ for all comparisons). Adverse events were more common with topiramate, including paresthesia (which occurred in over 50% of those on the drug), taste perversion, anorexia and difficulty with concentration. In general, however, the drug was safe and consistently efficacious for treating alcohol dependence (*JAMA*. 2007;298:1641-1651). An accompanying editorial points out that the benefits of topiramate were still increasing at the end of the study, indicating the longer treatment may be more effective (*JAMA*. 2007;298:1691-1692).

FDA Actions

The FDA has announced new warnings on phosphodiesterase type 5 inhibitors regarding hearing loss. The drugs include sildenafil (Viagra, Revatio), tadalafil (Cialis) and vardenafil (Levitra). The agency has received 29 cases of sudden hearing loss associated with use of the drugs dating back to 1996. Most cases were unilateral and temporary.

Modafinil (Provigil) has also been the subject of new warnings including serous rashes and psychiatric symptoms. The drug, which is used for narcolepsy, obstructive sleep apnea, shiftwork disorder, and multiple sclerosis, has been associated with severe rashes including Stevens-Johnson syndrome and toxic epidermal necrolysis. The FDA suggested caution should be exercised when modafinil is given to patients with a history of psychosis, depression, or mania.

An FDA advisory panel has recommended restricting childhood cold medications to children over the age of six years. They also recommend strong limits on marketing these products for younger children. This follows a voluntary withdrawal from the market of infant cough and cold medications by most manufacturers of these products. Voluntary withdrawal involves medications used in children younger than two years. The drugs that contain decongestants and antihistamines have been associated with more than one hundred deaths since 1969. ■

NEUROLOGY ALERT®
A monthly survey of developments in neurologic medicine

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NA120107TM

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