AMERICAN HEALTH CONSULTANTS® A Medical Economics Company

NEUROLOGY ALERT®

A monthly survey of developments in neurologic medicine

American Health Consultants Home Page—http://www.ahcpub.com CME for Physicians—http://www.cmeweb.com

EDITOR
Fred Plum, MD

ASSOCIATE EDITOR
John J. Caronna, MD
Vice-Chairman, Department of Neurology, Cornell University Medical Center; Professor of Clinical Neurology, New York Hospital

ASSISTANT EDITORS
Brian R. Apatoff, MD, PhD
Assistant Professor of Neurology, New York Presbyterian Hospital-Cornell Campus

Jeffrey Reich, MD
Assistant Professor of Neurology, New York Presbyterian Hospital-Cornell Campus

Norman R. Relkin, MD, PhD
Associate Professor of Clinical Neurology and Neuroscience, New York Presbyterian Hospital-Cornell Campus

Michael Rubin, MD
Associate Professor of Clinical Neurology New York Presbyterian Hospital-Cornell Campus

EDITORIAL ADVISORY BOARD
J. Richard Baringer, MD
Chairman, Department of Neurology; University of Utah College of Medicine

James A. Ferrendelli, MD
Chairman, Department of Neurology, University of Texas, Houston Medical School

Lawrence F. Marshall, MD
Chief, Division of Neurosurgery University of California-San Diego School of Medicine

Joseph B. Martin, MD, PhD
Dean of the Faculty of Medicine, Harvard Medical School

Jerome B. Posner, MD
Professor of Neurology Cornell Medical School Chairman, Department of Neurology, Memorial Sloan-Kettering Cancer Center

Special Clinical Projects
Gideon Bosker, FACEP
Assistant Clinical Professor Section of Emergency Services Yale School of Medicine

Role of Streptococcal Infection in Tourette Syndrome and Other Neuropsychiatric Disease

ABSTRACTS & COMMENTARY

Sources: Singer HS, et al. Antibodies against human putamen in children with Tourette syndrome. *Neurology* 1998;50:1618-1624; Kurlan R. Tourette's syndrome and 'PANDAS.' *Neurology* 1998;50:1530-1534; Garvey MA, et al. PANDAS: The search for environmental triggers of pediatric neuropsychiatric disorders. Lessons from rheumatic fever. *J Child Neurol* 1998;13:413-423; Hall MC, et al. Acute disseminated encephalomyelitis-like syndrome following group A beta-hemolytic streptococcal infection. *J Child Neurol* 1998;13:354-356; DiFazio MP, et al. Acute myoclonus secondary to group A beta-hemolytic streptococcus infection: A PANDAS variant. *J Child Neurol* 1998;13:516-518; Sanberg PR, et al. Treatment of Tourette's syndrome with mecamylamine. *Lancet* 1998;352:705-706.

Since the original description of sydenham's chorea (sc) many decades ago, a growing appreciation has emerged of the complexity of neurologic disease that may be related to streptococcal infection. The acronym PANDAS (pediatric autoimmune neuropsychiatric disorders associated with streptococcal infection) is a relatively new diagnostic construct to describe this spectrum of disease.

Several investigators have presented converging lines of evidence for a role of streptococcal infection in triggering Tourette syndrome (TS), obsessive-compulsive disorder (OCD) and other neuropsychiatric disease. Using standard ELISA and Western blot techniques, Singer and colleagues tested serum from 41 patients with TS (33 boys, 8 girls; mean age 11.3 years) and 39 controls (22 boys, 17 girls; mean age 12.1 years) for immune reactivity against human caudate, putamen, and globus pallidus. TS patients generated a significant increase in antineuronal antibodies, largely against putamen and caudate, compared to controls. Markers for streptococcal infection such as antistreptolysin O (ASO) titers were often equivocal.

DiFazio and colleagues reported three male patients, ages 5, 10, and 12 years, who developed a variety of myoclonic movement disorders associated with occult streptococcal infection. Only one

INSIDE

patient was culture positive, but all had high ASO and anti-DNAase B titers. The myoclonus was effectively treated with erythromycin or penicillin, and recurred with subsequent reinfection with streptococcus. Similarly, Hall et al reported a case of an 11-year-old boy who, one week following group A beta-hemolytic streptococcal pharyngitis, developed paraparesis with a post-infectious encephalomyelitis. The patient responded well to antibiotics and corticosteroids.

Sanberg et al reported a retrospective case series of 13 Tourette's patients treated with the nicotinic antagonist mecamylamine 2.5-5 mg/d, alone or in combination with haloperidol or sertraline. Four were adults (one female; mean age 34 years) and nine were children (one female; mean age 14 years). Eleven of the 13 improved significantly in motor and vocal tics, as well as behavioral complaints such as irritability and aggression.

COMMENTARY

Garvey et al and Kurlan provide excellent reviews of TS, tic disorders, and associated behavioral disturbance such as OCD that appear to arise from post-infectious autoimmune mechanisms. Thus, in addition to genetic factors that may determine a predisposition to TS, there appear to be important environmental triggers. An immune response generated against streptococcal antigens may crossreact with neuronal epitopes in the basal ganglia to cause neurological dysfunction. Trifiletti and colleagues at Cornell University Medical College have preliminarily identified a 83-kd brain protein by immunoblot analysis that seems to be recognized by antibodies in the serum of TS and OCD patients (*Ann Neurol* 1998;44:561).

The clinical therapeutic significance of these findings is important. Physicians now recognize the importance of penicillin prophylaxis for group A beta-hemolytic streptococcal infections in avoiding neurologic as well as cardiac complications. Undiagnosed streptococcal infection should always be considered in young patients presenting with new TS, OCD, SC, or other unusual movement disorders. Rather than using harsh neuroleptics for symptomatic management of TS or OCD, investigators are using immunomodulatory therapies such as corticosteroids, IVIG, and plasmapheresis with suggestion of benefit in small uncontrolled trials. Larger numbers of patients in carefully conducted studies will be required to assess the efficacy of these immune approaches that carry significant risks. Until then, pharmacologic agents such as the nicotinic drug mecamylamine may provide better symptomatic control. **—ba**

Recent investigations have demonstrated a relationship between streptococcal infection and auto-immune-precipitated neurological disease in children. Which of the following disorders has *not* been verified in this respect?

a. Chorea
b. Recurrent myoclonus
c. Tourette syndrome
d. Generalized epilepsy
e. Myelitis

Neurology Alert, ISSN 0741-4234, is published monthly by American Health Consultants, 3525 Piedmont Rd., NE, Bldg. 6, Suite 400, Atlanta, GA 30305.

GROUP PUBLISHER: Donald R. Johnston.
EXECUTIVE EDITOR: Glen Harris.
ASSISTANT MANAGING EDITOR: Robin Mason.
COPY EDITOR: Neill Larmore.

GST Registration Number: R128870672.
Second class postage paid at Atlanta, GA.
POSTMASTER: Send address changes to ***Neurology Alert***, P.O. Box 740059, Atlanta, GA 30374.

Copyright © 1999 by American Health Consultants. All rights reserved. No part of this newsletter may be reproduced in any form or incorporated into any information-retrieval system without the written permission of the copyright owner.

Back issues: $33. Missing issues will be fulfilled by Customer Service free of charge when contacted within one month of the missing issue's date.

This is an educational publication designed to present scientific information and opinion to health professionals, to stimulate thought, and further investigation. It does not provide advice regarding medical diagnosis or treatment for any individual case. It is not intended for use by the layman.

Subscriber Information

Customer Service: 1-800-688-2421.
Customer Service E-Mail Address: custserv@ahcpub.com
Editorial E-Mail Address: neill.larmore@medec.com
World-Wide Web: http://www.ahcpub.com

Subscription Prices

United States
$199 per year (Student/Resident rate: $100).

Multiple Copies
1-9 additional copies: $100 each. 10 or more copies: $60 each.

Outside the United States
$229 per year plus GST (Student/Resident rate: $110 plus GST).

Accreditation

American Health Consultants is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to sponsor CME for physicians. American Health Consultants designates this CME activity for 20 credit hours of Category 1 of the Physician's Recognition Award of the AMA. This CME activity was planned and produced in accordance with the ACCME Essentials.
For CME credit, add $50.

Questions & Comments

Please call **Robin Mason,** Assistant Managing Editor, at (404) 262-5517 or **Neill Larmore** at (404) 262-5480 between 8:30 a.m. and 4:30 p.m. ET, Monday-Friday.

Statement of Financial Disclosure

American Health Consultants does not receive material commercial support for any of its continuing medical education publications. In order to reveal any potential bias in this publication, and in accordance with Accreditation Council for Continuing Medical Education guidelines, a statement of financial disclosure of editorial board members is published with the annual index.

Midlife Factors that Affect Quality of Life in Old Age

ABSTRACTS & COMMENTARY

Sources: Reed DM, et al. Predictors of healthy aging in men with high life expectancies. *Am J Public Health* 1998;88: 1463-1468; Swan GE, et al. Association of midlife blood pressure to late-life cognitive decline and brain morphology. *Neurology* 1998;51:986-993.

Healthy aging, defined as surviving to late life free of major life-threatening illnesses and maintaining the ability to function physically and mentally, has become a medical issue of critical importance as the size of the population 65 years of age and older increases. Chronic disease and disability in the elderly have led to unprecedented increases in the cost of med-

ical care. The result is an important need to identify modifiable risk factors for disease and to use this information as the basis for systematic interventions designed to enhance the health of the elderly.

Reed and associates sought to identify risk factors that predict staying healthy in old age. They studied men of Japanese ancestry living in Hawaii, a group with one of the highest life expectancies in the world, at more than 79 years. More than 8000 men were followed for 28 years with repeat examinations and surveillance for deaths and incident clinical illness. Of 6505 healthy men at baseline, 39% died prior to the final examination. Among the 3263 survivors, 41% remained free of major illness, 40% remained free of both physical and cognitive impairment, and 19% were free of both illness and impairment.

The most consistent predictors of healthy aging were: low blood pressure, low serum glucose, not smoking cigarettes, and not being obese. High forced expiratory volume and low alcohol intake were strong predictors of survival, but were not independently related to the other outcomes of freedom from clinical illness and impairment. Physical activity measurements were not associated with any of the outcomes. *(See Table.)* Reed et al concluded that much of the illness and disability in the elderly is related to risk factors present at midlife.

Table

Predictors of Healthy Aging

Biologic Measures	Survival	Function
High blood pressure	↓	↓
High serum glucose	↓	↓
Obesity	↓	↓
Grip strength	0	↑
Lung function	↑	0
Health Habits		
Cigarette use	↓	↓
Physical activity	0	0
Alcohol use	↓	0

↓ = Indirect association
↑ = Statistically significant direct association
0 = No significant association

The study of Swan and associates supports the thesis that midlife risk factors affect old-age health. Swan et al investigated the association between midlife systolic blood pressure (SBP) and late-life cognitive decline and brain morphology. The present study included 392 surviving members of an earlier study in whom SBP had been measured in 1970, 1980, and 1985. They underwent an additional examination, including SBP measurement, neurobehavioral testing, and brain MRI obtained between 1995 and 1997. Subjects with high midlife SBP experienced a greater decline in cognitive performance and had more white matter hyperintensities (WMHI) in late life than did those with low midlife SBP. Decreased brain parenchyma and increased WMHI were associated with a late-life decline in neurobehavioral function that was independent of age, education, and baseline levels of cognition. Therefore, Swan et al concluded that midlife SBP is a significant predictor of both brain atrophy and a decline in cognitive function in late life.

COMMENTARY

In the elderly, beyond biological aging, most physical disability and need for long-term medical care results from clinical illnesses such as heart disease, stroke, diabetes, arthritis, blindness and hip fracture. Both the studies abstracted above indicate that much of the underlying disease pathology in the elderly begins in young or middle adult life. Reed et al's study indicates that low levels of known risk factors such as hypertension, diabetes, smoking, and obesity, as well as an absence of chronic diseases consistently predict healthy aging. Swan et al provide supporting evidence of the negative effect of hypertension on brain structure, midlife SHP leading to decreased brain volume, increased WMHI, and cognitive decline.

These two studies reflect a growing recognition of the importance of disease prevention. Poor health late in life is not inevitable and modifiable risk factors make a greater contribution than was previously thought. It is never too late to institute blood pressure reduction and stop smoking in the elderly: the earlier the therapeutic intervention, the greater the dividends later in life. **—jjc**

Each of the following midlife traits is a predictor of healthy aging *except*:

a. low blood pressure.
b. isolated systolic hypertension.
c. low serum glucose.
d. low alcohol intake.
e. not smoking cigarettes.

Now that the Trials are Finished and Quantitated, What Fraction of Carotid Endarterectomies Reflects Mere Entrepreneurism?

ABSTRACTS & COMMENTARY

Sources: Barnett HJM, et al. Benefit of carotid endarterecto-

my in patients with symptomatic moderate or severe stenosis. *N Engl J Med* 1998;339:1415-1425; Tu JV, et al. The fall and rise of carotid endarterectomy in the United States and Canada. *N Engl J Med* 1998;339:1441-1447; Chassin MR. Appropriate use of carotid endarterectomy. Editorial. *N Engl J Med* 1998;339:1468-1471.

During the past 20 years, carotid endarterectomy has been a popular, but largely unregulated, surgical procedure in the United States and less enthusiastically in Canada and Europe. The operation's incidence in the United States reached a peak of 107,000 during 1985. Then, after the initiation of carefully conducted clinical trials, the incidence first fell to 80,000 and then to 60,000 between 1986 and 1991. Subsequently, a steady operative climb has occurred to reach 120,000 operations in 1996.

All well controlled trials have focused on patients known to have experienced within the previous 180 days either non-crippling stroke(s) or TIAs ipsilateral to the potential carotid stenosis. Outcomes of these proceedings were measured at least at two and five years after onset. Kaplan-Meier curves of outcomes indicated a perioperative risk of 2-6% of associated severe stroke and/or death within 30 days following surgical treatment. From that point forward, symptoms related to ipsilateral carotid artery endarterectomy showed significant reductions in stroke or death compared to non-operated controls after the first two to three postoperative years. After this time, new strokes in both operated and non-operated patients occurred at an annual rate. *(See Table).*

Table

Surgical Risk Reduction for Carotid Endarterectomies

Stenosis	Symptomatic Study Groups	Risk Reduction Point (P =)	% Surgical Complication
> 70% North American (NASCET)		16.5 @ 2 yr. < 0.001	5.8
> 60% European (ECST)		11.6 @ 3 yr. < 0.001	4.8
50-69%	NASCET	10.1 @ 5 yr. < 0.005	6.7
< 50%	NASCET	0.8 @ 5 yr. < 0.97	6.7
> 60%	ACAS (Asymptomatic)	6.3 @ 5 yr. < 0.08	2.3

(Surgical complications = strokes or deaths in 30 post-op days. Table adapted from Chassin MR. *N Engl J Med* 1998;339:1468-1471.)

COMMENTARY

Tu and associates evaluate the above surveys that favored endarterectomy in patients who preoperatively had recently experienced either non-severe strokes or TIAs ipsilateral to the carotid artery narrowed more than 60%. However, they question the force behind the increasing gap that distinguishes the Canadian annual incidence of 40,000 or less endarterectomies since 1983 compared to the current lofty numbers in the United States. The age rate of endarterectomy in California (CA) and New York (NY) differed sharply from Ontario (ONT). Incidence of endarterectomy per 100,000 in patients 65 years and older was as follows: CA: 1989 = 163, 1995 = 277; NY: 1989 = 85, 1995 = 239; ONT: 1989 = 26, 1995 = 86.

The costs and cost effectiveness of these large jumps in operative selection deserves better justification than simply the appearance of internal carotid artery stenosis more than 6% with or without corollary symptoms.

Neurology Alert editor asks the following, logical questions: Why do we have no outcome statistics justifying this huge surgical effort in the United States compared to Canada? How many of these operations were performed on asymptomatic patients? What was the recorded success rate of the surgeons and how many neurologists participated in the choice and the eventual results? Regrettably, no such answers exist. Only one study (ACAS) has analyzed outcome in patients with asymptomatic stenosis. Its results indicate that despite only a 2.3% perioperative risk, the procedure rescued only one severe stroke and no deaths among the subscribers. Without such data, and in the presence of all the clinical trials on symptomatic patients, one can't help but wonder why the insurance companies don't demand such cost/benefit facts.

Three additional questions arise: 1) Without knowledge of five-year outcomes associated with asymptomatic carotid stenosis, how can one estimate the future benefit of carotid endarterectomy in these large numbers of preoperatively asymptomatic patients? Certainly, surgical skill, hospital practice, and public health sources should require such data. 2) What were the perioperative 30-day complications in these patients?

3) Given that Canada and the United States have adult populations with relatively similar health, why do Canadian surgeons perform only one-third the number of endarterectomies performed in the United States? We recognize that it is impolite to ask, but who besides the surgeons' are benefitting from this huge operative venture? **—fp**

Which of the following statements is correct?

a. Any internal carotid artery stenosis more than 50% provides a risk factor in stroke.
b. Data indicate that all patients with carotid stenosis more than 70% deserve endarterectomy.
c. Patients with carotid stenosis more than 60% who have suffered an ipsilateral TIA or stroke within the past six months are strong candidates for endarterectomy.
d. Data indicate that all patients with carotid stenosis more than

80% deserve endarterectomy of the stenosis.

Evidence of Subtle Structural Abnormalities in Idiopathic Generalized Epilepsy

ABSTRACT & COMMENTARY

Source: Woermann FG, et al. Quantitative MRI in patients with idiopathic generalized epilepsy—Evidence of widespread cerebral structural changes. *Brain* 1998;121:1661-1667.

In contrast to focal epilepsies that are associated with structural brain lesions, such as areas of cortical dysplasia, scarring or hippocampal sclerosis, idiopathic generalized epilepsies (IGE) are believed to arise from largely unclear genetic factors. In fact, the International League Against Epilepsy (ILAE) definition of idiopathic generalized epilepsies specifies that neuroradiological abnormalities should be absent in these patients (Commission of Classification and Terminology of the ILAE, *Epilepsia* 1985;26:268-278). Histopathological studies of patients with IGE, though rare, have identified microscopic structural changes termed microdysgenesis that consists mainly of excess neurons in the molecular layer of cortex (Meencke HJ. *Epilepsia* 1985;26:250-254). Increased numbers of ectopic neurons in the subpial space and in the subcortical white matter have been described (Meecke HJ, Janz D. *Epilepsia* 1984;25:8-21). The number of neuropathological studies in patients with IGE is small, however, and the finding of microdysgenesis associated with IGE is not without controversy (Lyon G, Gastaut H. *Epilepsia* 1985;26:365-367).

Woermann and colleagues bring quantitative MRI to bear with the question of whether subtle structural changes are present in the brains of patients with IGE. With the ability to image a volume less than a millimeter cubed, Woermann et al applied software methods to the analysis of the MRI images to measure cortical gray matter volume separately from the combined subcortical white and gray matter volume. Comparing a population of 45 patients with IGE, which was comprised of 20 patients with juvenile myoclonic epilepsy, 10 patients with childhood absence epilepsy, 10 patients with juvenile absence epilepsy, and five patients with tonic-clonic seizures on awakening, Woermann et al found mean total cerebral volume and the mean normalized cortical volume (expressed as a percentage of total brain volume) did not differ significantly from a population of 30 normal controls.

When regional differences of cortical and subcortical volumes were compared, however, structurally abnormal brains were detected in 15 of the 45 patients. To accomplish the identification of regional abnormalities, Woermann et al divided the cerebral volume of patients and controls into 10 slices of equal thickness arranged from anterior to posterior. Each slice consisted of equivalent portions of the right and left hemispheres, so that a total of 20 volumes of interest, 10 slices times two hemispheres were used. Volumes of interest were all normalized as a percentage of the total cerebral volume to permit comparison between individuals. The regional cortical and subcortical normalized volumes were extracted and used to compute several additional parameters that identified subtle variations in anatomy between patients and controls. A total of 80 different regional measurements were calculated for each patient or control. These measurements consisted of the normalized cortical and subcortical volumes in each volume of interest, the ratios of ipsilateral cortical to subcortical matter in volumes of interest, and the ratios of ipsilateral to contralateral volumes of homologous volumes of interest (e.g., ipsilateral cortical volume to contralateral cortical volume). The normal range was defined as the range of values within three standard deviations of the mean value of each measurement in the control population. Three of the 30 individuals in the control group had one abnormal measurement, while the rest of the control group had no abnormalities. Since three individuals in the control group had one abnormal measurement, the presence of two or more abnormal measurements was required to identify a structurally abnormal brain.

In the group of 15 IGE patients who met the criteria for structurally abnormal brains, there were an average of 5.4 abnormal measurements per patient. By epilepsy subtypes, eight of the identified patients had juvenile myoclonic epilepsy, four had juvenile absence epilepsy, one had childhood absence epilepsy, and two had tonic-clonic seizures on awakening. The majority of abnormalties were found in the central volumes of interest. Half of the abnormal measurements resulted from an increase in the ratio of the regional cortical volume to the ipsilateral subcortical volume. The distribution of regional asymmetries accounting for the remaining abnormal measurements is not reported.

Woermann et al interpret the increase in the regional ratio of cortical volume to subcortical volume by suggesting altered interneuronal connectivity in the cortex of patients with IGE. They argue that an area of abnor-

mal cortex may contain increased neurons, neuronal volumes, or neuropil, or may project fewer or smaller axons to the subcortical volume. Either scenario, it is argued, will result in altered connections between neurons. Cortical hyperexcitability has been demonstrated in patients with IGE (see citations given by Woermann et al). Woermann et al go on to suggest that microdysgenesis may be the origin of the regional structural asymmetries detected by their methods and may in turn result in cortical hyperexcitability.

COMMENTARY

This study brings forward several interesting findings. If one takes the view that cortical development is a largely radially symmetrical process guided by global genetic influences, the presence of regional heterogeneities and asymmetries in the cortical and subcortical matter detected by MRI is somewhat unexpected. The observation that the majority of abnormalities were found in the central cortical and subcortical area may help identify the genetic trigger responsible for IGE. For example, it is possible that the abnormality in IGE may originate in the genetic factors guiding local cortical differentiation, such as the creation of the Betz cells in layer V of the motor cortex. It is also interesting that 10% of normals had one regional abnormality. While it is possible that the detection of abnormalities in normals results from statistical noise, it is provocative to consider that IGE might represent the extreme of a spectrum of genetic traits.

The findings described by Woermann et al are likely to fuel the controversy between proponents and opponents of the microdysgenesis etiology of idiopathic generalized epilepsies. There are results to support both points of view. The presence of regional abnormalities in one-third of patients with IGE supports the tenet that genetic miswiring of the cortex may be a factor in idiopathic generalized epilepsy. However, the presence of regional abnormalities in 10% of the controls, and the failure to detect a structurally abnormal brain in two-thirds of patients casts doubt on the possibility that microdysgenesis is the major cause of IGE. Of course, by altering their definition of the normal range, here taken to be values that lay within three standard deviations of the mean, it may be possible to detect more abnormalities in the patient population. It is likely, however, that a more stringent definition of the normal range would increase the detection of abnormalities in the normal controls.

If one accepts the proposition that microdysgenesis is a cause of IGE, structurally abnormal cortex or subcortical regions should also cause abnormal cortical and subcortical function and changes in the EEG background of IGE patients. Abnormal background activity of EEG is the expected result of dysfunction of the cortex or subcortical white or gray matter. One of the hallmarks, however, of idiopathic generalized epilepsies is that the background EEG is normal. (Daly, Pedley. *Current Practice of Clinical Electroencephalography*, New York: Raven Press; 1990). The presence of regional slowing of the background, as might be expected from a region of cortical microdysplasia, is not seen in patients with IGE. Generalized background slowing, a feature of dysfunction in the subcortical gray matter, is also not typically seen in patients with IGE. Clinically, the patients with IGE also usually develop normal intellect and neurologic function (Wyllie. *The Treatment of Epilepsy*, Baltimore: Williams and Wilkins; 1997), which might not be expected in patients with a congenitally dysfunctional cortex.

As with any thoughtful work, the results of Woermann et al raise more questions than they answer. Nevertheless, in bringing the modern tools of MRI and computer analysis to the problems of neuropathology, Woermann et al have devised an alternative to, though not a substitute for, autopsy studies. One may hope that in the future, methods will be developed that may provide better radiographic analysis of the brain. Nevertheless, it is equally clear that there is an ongoing need for autopsy specimens for modern pathologic study. It is also premature to settle on microdysgenesis as the cause of the idiopathic generalized epilepsies. The etiology of idiopathic generalized epilepsies remains open and will likely require the contributions of electrophysiology, neuroradiology, and neuropathology before it can be satisfactorily answered. **—fl & sm** *(Dr. Lado is an EEG Fellow, Department of Neurology, Montefiore Medical Center-Albert Einstein College of Medicine, Bronx, NY. Dr. Moshe is Professor and Director, Pediatric Neurology and Clinical Neurophysiology, Department of Neurology, Montefiore Medical Center-Albert Einstein College of Medicine, Bronx, NY.)*

CNS Involvement in Herpes Zoster

ABSTRACT & COMMENTARY

Source: Haanpaa M, et al. CSF and MRI findings in patients with acute herpes zoster. *Neurology* 1998;51: 1405-1411.

Fifty immunocompetent patients, 22 men and 28 women, with acute herpes zoster but without CNS

complications including signs of meningeal irritation, encephalitis, or myelitis underwent CSF study (n = 46), MRI (n = 16), or both (n = 16) to correlate laboratory abnormalities with clinical findings and outcomes. CSF analysis included measurement of cell count, total protein, IgG index, oligoclonal banding (OCB), IgG and IgM anti-varicella zoster virus (VZV) antibodies, and PCR assay for VZV DNA. MR imaging comprised cranial (n = 12) or cervical studies (n = 4), for cranial or cervical VZV eruptions, respectively, but due to flow artifacts, thoracic and lumbar cord MRI scans were not performed. Statistical analysis included Fisher's exact test, log-linear modeling, and logistic regression.

CSF pleocytosis, present in 46% (21/46) overall, and seen in the first sample in 17 patients, was present in the first sample in seven of seven patients with HZ-related MR abnormalities but in only one of four patients with a normal MRI (P = 0.01). OCB was present in 9% (4/43), two of which had HZ-related MR findings. Approximately 25% each had elevated CSF protein, anti-VZV IgG antibodies, or VZV DNA, but this did not correlate with clinical outcome or MR abnormalities. IgG index was abnormal in only one of 42 patients. Overall, CSF analysis demonstrated at least one abnormality in 61% (28/46), and MRI findings attributable to HZV were seen in 56% (9/16). None of the MRIs were enhanced with gadolinium, implying only mild inflammation or necrosis unlikely to lead to permanent changes. Interestingly, five of nine patients with abnormal MR scans developed post-herpetic neuralgia (PHN) within three months. PHN affected none of seven with normal MR imaging. The numbers are too small to be predictive but if extended to larger studies, may influence the initiation of treatment for HZ and prevention of PHN.

COMMENTARY

Pain control in PHN remains challenging. Standard therapy includes amitriptyline (AT) but lack of efficacy (up to 50%) and unpleasant side effects limit its usefulness (Watson CPN. *Neurology* 1995;45(suppl 8):58-60). In a double-blind, randomized cross-over trial of 31 patients suffering moderately severe PHN for at least half-a-day for three or more months, amitriptyline was compared to nortriptyline (NT), its major noradrenergic metabolite, for efficacy and side effect profile. Patients with cardiac disease, seizures, brain damage, alcoholism, and severe depression were excluded. Treatment for five weeks, with a two week wash-out period before cross-over to the other agent, was initiated at 10-20 mg and increased by 10 mg increments every 3-5 days. Primary outcome measures, taken weekly, included pain evaluation, pain relief, and sleep (all measured using a visual analogue score), depression (using the Beck Depression Inventory), side effects, disability, and overall satisfaction.

AT and NT equally controlled pain in about 50% showing no significant difference with respect to mood, disability, satisfaction, or use of concomitant analgesic medication. Mean dose was 58 mg and 75 mg for AT and NT, respectively, among responders, and 68 mg and 97 mg among non-responders. Side effects were more common in the AT group, including dry mouth, constipation, and drowsiness, but tolerability was comparable in both groups.

In a similarly designed double-blind crossover study of 38 PHN patients (including 16 from the AT trial!), controlled-release oxycodone, a semi-synthetic opioid analgesic, 10 mg (with titration up to a possible 30 mg) twice-a-day was found to be significantly more effective than placebo for relief of steady pain, paroxysmal brief pain, allodynia, disability, global effectiveness, and patient preference. Constipation, nausea, and sedation were more common with oxycodone but did not overly contribute to drug discontinuation. Oxycodone and tricyclic antidepresssants appear comparable in their analgesic efficacy for PHN. **—mr**

With Herpes zoster rash but in the absence of CNS disease, which one of the following is correct:

a. CSF pleocytosis is present in about 10%.
b. oligoclonal bands are present in about 25%.
c. approximately 50% have elevated CSF protein.
d. approximately 40% have elevated anti-VZV IgG antibodies.
e. MRI findings attributable to HZV may be seen in approximately 50-60%.

Brief Alert

Cardiac Disease in Muscular Dystrophy

Source: Laforet P, et al. Cardiac involvement in genetically confirmed facioscapulohumeral muscular dystrophy. *Neurology* 1998;51:1454-1456.

Facioscapulohumeral muscular dystrophy (FSHMD), an autosomal dominant myopathy mapped to the telomeric end of chromosome 4q35, shows almost complete penetrance, with a variable rate of progression, but uniform evolution in all patients. Often asymmetric, it begins in the facial and shoulder girdle muscles, later spreads to abdominal, foot extensor, and pelvic girdle muscles, and rarely is associated with symptomatic hearing loss and retinopathy (Padberg GW,

et al. *Muscle Nerve* 1998;Suppl 7;S25). Cardiac involvement has usually been ascribed to unrelated, coincidental illness but this may now require reconsideration (Griggs RC, et al. *Evaluation and Treatment of Myopathies*. CNS Series. Philadelphia: FA Davis Company; 1995:122-126). Among 100 clinically and molecularly defined FSHMD patients, five demonstrated significant cardiac rhythm abnormalities unrelated to myopathic disease or cardiovascular risk factors. This includes supraventricular arrhythmia (n = 3), two of which had conduction defects, and one each with arrythmogenic right ventricular cardiomyopathy, hitherto unreported in myopathic patients, severe atrioventricular block requiring pacemaker insertion, and supraventricular arrhythmia with palpitations. Five percent of FSHMD patients appear to be at risk for coincident cardiac arrythmias. EKG study and follow-up is warranted. **—mr**

Cardiac disease is present in:

a. 5% of FSHMD patients.
b. 10% of FSHMD patients.
c. 15% of FSHMD patients.
d. 20% of FSHMD patients.
e. 25% of FSHMD patients.

Early Detection of Bulbar Involvement in ALS

Source: Finsterer J, et al. Needle electromyography of bulbar muscles in patients with amyotrophic lateral sclerosis: Evidence of subclinical involvement. *Neurology* 1998;51: 1417-1422.

Electromyographic quantitative motor unit potential analysis (MUPA) and peak ratio interference patterns (PRIP) were analyzed in the masseter, frontalis, and sternocleidomastoid muscles in nine amyotrophic lateral sclerosis (ALS) patients to determine whether these electrodiagnostic techniques detected subclinical bulbar involvement in ALS. Twenty-one healthy subjects served as controls and MUPA, but not PRIP, was found to be sensitive for subclinical disease. Early diagnosis in ALS should not prevent the search for a confirmatory opinion or alternative diagnosis, but it may allow these patients earlier access into experimental therapeutic trials in the race for a cure. **—mr**

Letter to the Editor

Concerning the November issue of *Neurology Alert* and the article "Antiepileptics During Pregnancy," one point that was not emphasized in the study performed in Iceland was that the incidence of major congenital malformations in epileptic mothers not treated with anti-epileptics was still greater than two-fold over the general population without epilepsy. I do think that this point was not made.

When dealing with epilepsy in general, we see a higher incidence of congenital malformations as opposed to the general population. The point was well made that with multiple anti-epileptics, there is a higher risk of malformation. The question must be raised as to whether the anti-epileptics add to the risk of major congenital malformations that may not by themselves increase the risk. The epilepsy itself may be a risk factor.

This point has been touched on in the past and women with epilepsy need to be aware of this fact since there is always a question as to whether it would be safer to be off the medication.

Sincerely,
Felix Brizuela, Jr., DO
Neurological Institute of Western Pennsylvania
Greensburg, PA

Response from Dr. Plum:

Thank you for your letter to the publishers of Neurology Alert pointing out that epileptic mothers not treated with anti-epileptics was greater than two times over the general population. As you might expect, I can't bring out all of the points from the literature in one small report and I must adhere to what the authors themselves have addressed. Nevertheless, I think it is quite clear by well carried out drug studies that anti-convulsants as a group not only increase the risk of malformations in epileptic mothers, but even more, some have a more grave influence than others.

I'm delighted that you're interested in reading Neurology Alert. We do our best to keep important things at our readers' fingertips.

Sincerely,
Fred Plum, MD

In Future Issues: Symptomatic Treatment of Painful Neuropathy