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## Two Forms of Unilateral Consistent Headache and Its Sources

ABSTRACTS & COMMENTARY

**Sources:** Bahra A, et al. *Neurology.* 2002;38:354-361; Pringsheim T. *Can J Neurol Sci.* 2002;29:33-40; Pareja JA, et al. *Cephalalgia.* 2001;21:940-946.

THESE 3 REPORTS INDIVIDUALLY DISCUSS PARTIAL REVIEWS OF classic paroxysmal headache (CH), its source, and its difference from hemicrania continua (HC). Bahra and colleagues discuss the broad clinical aspects of CH on the basis of clinical symptoms alone. Pringsheim provides an interesting and informative description of the pathophysiology which describes the genetic factors as well as some of the patterns behind the development of CH. Pareja and colleagues focus on a specific cluster disorder called HC which consistently responds to the single, sustained effective treatment of indomethacin.

**Classic Paroxysmal Headache.** Bahra et al evaluated 230 patients with unilateral CH. One hundred sixty-six (72%) were men, 64 (28%) women. Pain affects men and women equally and frequently involves mostly the retro-orbital, temporal, dental, forehead, jaw and, less frequently, lower areas of the face. All patients suffer only a consistently unilateral pain with 60% located on the right side of the head. Associated with the pain, autonomic activity includes tearing, conjunctival injection, lid ptosis, and rhinorrhea. Half the patients become nauseated and 93% become physically restless during the attack. Less intense symptoms include nausea, photophobia, vomiting (few), annoyance by light, noise, or drinking alcohol. CH occurs during large time periods once or twice a year. Average individual bouts last a maximum-minimum of 159-72 minutes and the mean number of attacks can occur 4-5 times in 24 hours. Most sieges of CH lasted about 8.6 weeks once a year with 43% of patients suffering their bouts in spring or autumn. The use of either tobacco smoking or any alcohol stimulates severe bursts. Nevertheless, most patients with cluster headache (67%) have continued to smoke, and 90% who took alcohol reported a triggered attack. Sixty of the 230 patients with CH reported previous symptoms of migraine and a third claimed a family history of migraine. Five percent indicated

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## INSIDE

a close family member who had migraine. No principal symptomatic differences affected males or females in any quality except by the overall number of men 2.5:1 to women. Only 5 women had cluster headache during pregnancy, but menopause had only a small effect on their suffering. Sumatriptan was ingested by oral (61%), subcutaneous (45%), or intranasal (14%) routes; half of the group had taken oral ergotamine agents.

Unfortunately, the only effective drug that acutely ameliorates cluster headache consists of subcutaneously injected sumatriptan immediately upon the onset of headache (Ekbom K. *N Engl J Med.* 1991;325:322-326). Gobel and colleagues, however, found 88% successful injection therapy during 2031 attacks in 52 affected sufferers (Gobel H, et al. *Neurology*. 1998;51:908-911). Inhalation of high concentrations of oxygen will quiet the attack, but clumsiness of the apparatus usually prevents its readiness. No oral drug has yet met the noninvasive challenge, although intranasal application of sumatriptan apparently halts cluster headache in less than an hour. Methysergide and lithium provide a certain degree of prevention against successive bouts of cluster headache, but methysergide may injure cardiopulmonary tissues if sustained more than a month or so. Oral verapamil carries some protection against close serial bursts.

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Dr. Pringsheim has summarized from the past literature that the ultimate source of cluster headaches comes from the period (PER) gene located on the X chromosone and the timeless (TIM) gene, both in the chromosone suprachiasmatic (STC) nucleus of the hypothalamus. This nucleus generates the proteins of PER and TIM which synthesize and bind together in retinal-delayed darkness (mostly sleep). As light appears in wakefulness, the TIM protein begins to degrade gradually until it ceases. When darkness reappears, TIM becomes maximally synthesized and, with PER, the circadian molecule pattern repeats its cycle. In the 4 annual, equal dark/light zones, the hypothalamic STC reaches its largest cell numbers near the Ides of March and September, thereby anticipating day/night equality of light. The suprachiasmatic nucleus regulates the melatonin protein generated by the pineal gland. Melatonin feeds from the pineal body to the STC nucleus that stimulates the superior cervical ganglia which sends more epinephrine back to the pineal gland. This then stimulates increased melatonin, which shifts the circadian clock. Recently, PET scanning has identified the specific area of the active STC circadian pacemaker in the hypothalamus.

About half or more of patients who suffer classic episodic cluster headaches do so in relation to the influence of the sunlight on their retinas and thalamic STC nucleus. Typical are the active bouts during the 7-10 days in early July or the similar period following the early days of January. Their "off" months usually come in April and October. Two thirds suffer nocturnal attacks with many relating to REM sleep. Most suffer abnormal sleep patterns even without the headaches. Leone and associates, however, have recently reported that 10 mg daily of melatonin significantly improved the intensity and number of attacks associated with cluster headaches (Leone M, et al. *Cephalalgia*. 1996;16:494-496).

**Classic Hemicrania Continua (HC).** HC is a relatively rare, spontaneously appearing year-round disorder consisting of the following: 1) HC, if not treated, consists of a moderate-to-severe regular, unilateral, and spontaneous head pain that is almost daily expressed throughout the year. 2) The pain consistently appears over their trigeminal sensory area and can be absolutely ameliorated only by steady, daily ingestion of indomethacin (Goadsby P, Lipton R. *Brain*. 1997;120:193-209). When headache and focal autonomic dysfunction appear, trigeminal autonomic activity may generate ipsilateral pupillary mitosis, tearing, lid ptosis, and rhinorrhea along with the resurgent pain. 3) Other patients with unilateral head-face pain

(HP) that continuously appears throughout long periods of the year may not receive relief from indomethacin. Pareja et al and your editor can identify examples of such unilateral headaches that may occur every day or so but are not responsive to indomethacin. These include repetitive unilateral migraine, recurrent dental problems, supraorbital neuralgia, cervicogenic headache, post-traumatic dysautonomic cephalalalgia, unilaterial tension-anxiety type headache, atypical facial pain, and temporal-mandibular joint disorders. Moderate psychological depression or anger also may evoke unilateral steady muscle pain. Many of these patients can be helped by other available non-narcotic drugs and over-the-counter medications. Like many patients with functional back pain, however, many patients with chronic bilateral headaches and some with unilateral ones, go on and on without finding any apparent particular agent of cause. **—FRED PLUM**

# Viral Encephalitis: A Deadly Differential Diagnosis

ABSTRACT & COMMENTARY

**Source:** Whitley RJ, Gnann JW. *Lancet.* 2002;359:507-512.

WHITLEY AND GNANN REVIEWED THE RECENT LITerature on viral encephalitis and present an up-to-date summary of the pathogenesis, clinical syndromes, diagnosis, and treatment of several familiar and unfamiliar viral encephalitides.

Viral encephalitis is an unusual but often deadly manifestation of human infection. For some viruses such as mumps, central nervous system (CNS) infection is a common but usually benign part of the syndrome. For others such as Japanese encephalitis, neurological disease is the most prominent clinical feature of systemic infection. In the case of rabies, infection inevitably and exclusively results in CNS disease. In contrast, herpes simplex virus (HSV) is a common pathogen but only rarely causes encephalitis.

In a nonepidemic setting, HSV is the most common viral encephalitis. Because specific antiviral therapy is available for HSV encephalitis, confirmation of the diagnosis is urgent. Fortunately, the commonly used neurodiagnostic tests including CT, MRI, and EEG can provide useful information in the assessment of encephalopathic patients. Evaluation of the CSF is essential in patients with viral encephalitis and usually reveals a predominantly mononuclear pleocytosis and increased levels of protein. The use of PCR applied to the CSF to detect viral nucleic acids has become the diagnostic method of choice for HSV and other viral infections of the CNS.

Worldwide, viruses transmitted to humans by the bites of arthropods, mosquitoes, and ticks are especially causes of encephalitis. In the United States, most cases of arthropod-borne encephalitis have been attributed to LaCrosse virus and St. Louis encephalitis (*see Table*). Beginning in August 1999, an epidemic of encephalitis due to West Nile virus occurred in and around New York City. West Nile virus encephalitis is a disease encountered in Africa, The Middle East, and Eastern Europe but had not been identified previously in the Western Hemisphere. The recurrence of additional cases of West Nile virus in North America during subsequent summers indicates that the virus has established an enzootic cycle of transmission involving migratory birds and mosquitoes. New outbreaks are likely throughout the United States.

## COMMENTARY

This useful review highlights the pathogenesis and clinical features of the familiar causes of viral encephalitis. In addition, Whitley and Gnann warn of high probability of future epidemics of encephalitis caused by previously unknown pathogens or as new manifestations of an increased virulence of known agents. Clinicians need to be aware of the broad spectrum of viral pathogens when assessing a patient presenting with possible acute viral encephalitis. **—JOHN J. CARONNA**

**Table**

**Selected Mosquito-Borne Arbovirus Encephalitides**

| Virus | Geographical Distribution in United States | Age-Group Affected | Mortality |
|---|---|---|---|
| Western Equine | West, Midwest | Infants, Adults | Moderate in infants |
| | | (> 50 years) | Low in adults |
| Eastern Equine | East, South | Children and Adults | > 30% |
| St. Louis | Central, West, South | Adults (> 50 years) | 20% |
| LaCrosse | Central, East | Children | 10-15% |
| West Nile | East Coast | Adults | Low |

*Table adapted from: Whitley RJ, Gnann JW. Lancet. 2002;359:507-512.*

# Visual Hallucinations in Lewy Body Disease

ABSTRACT & COMMENTARY

**Source:** Harding AJ, et al. *Brain.* 2002;125:391-403.

THE PATHOLOGIC HALLMARK OF PARKINSON'S DISease (PD) is the accumulation of Lewy bodies within the substantia nigra. Improvements in immunohistochemistry in the last decade have revealed that Lewy bodies are often abundant in the cerebral cortex as well as the midbrain. Investigators have tried to separate patients with PD, Parkinson's disease with late developing dementia (PDD), and dementia with Lewy bodies (DLB) based on their clinical features, emphasizing the presence of fluctuating cognition and visual hallucinations in DLB, and the late development of dementia in PDD. In fact, there is considerable overlap between DLB and PDD, and it is often difficult to differentiate patients with PD who have hallucinations and mild cognitive impairment from those with developing DLB.

One might ask why neurologists should be concerned about these distinctions at all. In fact, the presence of cognitive decline and formed persistent visual hallucinations is an ominous clinical feature for patients and their families, often leading to permanent assistance in the home or even placement in a nursing home. Protecting Parkinson patients from paranoid ideation or frightening visual hallucinations is one of the most important responsibilities of neurologists who care for patients with that disease.

The present study reflects a comprehensive, prospective, clinico-pathologic correlation of parkinsonian features with pathologic findings in a cohort of patients studied in Australia. Harding and colleagues prospectively examined patients using a wide variety of clinical rating instruments to assess motor performance, cognition, behavior, and the nature of visual hallucinations. After death, brains were examined for the presence and density of cortical Lewy bodies.

The majority of DLB and PDD cases had visual hallucinations early in their course, whereas less than one quarter of PD cases had hallucinations. Cognitive fluctuations were present in most DLB cases, and significantly less frequently in PDD and PD. However, neither visual hallucinations nor cognitive fluctuations were predictive of DLB, although their absence early in the disease course was highly suggestive of PD.

The highest density of cortical Lewy bodies in DLB occurred in the amygdala, anterior cingulate, inferior temporal, and parahippocampal regions. The sum of combined density of Lewy bodies in the cortex did not correlate with the severity of dementia. Lewy bodies in the parahippocampus and inferior temporal cortex were highly predictive of formed visual hallucinations.

## COMMENTARY

This study is one of the most comprehensive attempts to correlate clinical and pathologic features in patients with Lewy body pathology. The primary finding that formed visual hallucinations suggest Lewy body pathology in the inferior temporal cortex, is the first association between visual hallucinations and cortical pathology. The study also demonstrates the clinical and pathologic overlap between patients with DLB and PDD. Although this issue is still subject to debate, the present study supports the idea that PD, PDD, and DLB represent different points on a pathologic continuum characterized by accumulation of Lewy bodies within the brain. —**STEVEN FRUCHT**

# The Current Status of Status Epilepticus

ABSTRACTS & COMMENTARY

**Sources:** Mayer SA, et al. *Arch Neurol.* 2002;59(2):205-210; Claassen J, et al. *Neurology.* 2002;58(1):139-142; Logroscino G, et al. *Neurology.* 2002;58(4):537-541.

MAYER AND COLLEAGUES ANALYZED 83 EPISODES OF status epilepticus (SE) in 74 patients presenting to the Columbia campus of New York Presbyterian Hospital. They identified 26 (31%) episodes defined as refractory status epilepticus (RSE) because of continuous or repetitive seizures that did not respond to first- and second-line anticonvulsant drug (ACD) therapy. Moreover, 11 of the 26 patients continued to have seizures after a third ACD was given. Univariate analysis was applied to find clinical factors associated with RSE. Those were followed by entering significant variables in a backward, stepwise logistic regression model to identify RSE independent risk factors. Only nonconvulsive SE (NCSE) and focal motor seizures at onset proved to be statistically significant in this model. Although mortality was not affected, hospital length of stay and Glascow Outcome Scale (GOS) score were increased in the RSE group relative to the 57 episodes of SE responsive to 1-2 ACDs.

The same data set were evaluated by Claassen and colleagues from the standpoint of finding predictors of

functional disability (16/69 nonfatal episodes of SE) and mortality (14 episodes) following SE. Hospital length of stay longer than 2 weeks and acute symptomatic seizures (defined as seizures related to a readily identifiable precipitant in a patient with no history of seizures), predicted worse GOS on hospital discharge compared to admission. Age older than 62 and, again, acute symptomatic seizures were independent predictors of mortality.

In another group looking at long-term mortality following an incident case of SE, Logroscino and colleagues found a cumulative mortality of 43% (n = 62) over 10 years among patients who had survived 30 days following SE (n = 145). The standardized mortality ratio (SMR) at 10 years was 2.8 for all 30-day survivors. The following clinical characteristics predicted a significant increase in mortality: SE duration lasting 24 hours or more, acute symptomatic etiology, and myoclonic SE.

### COMMENTARY

Sorting through all the multivariate analyses presented in these and earlier investigations, *Neurology Alert* recognizes 2 practical considerations. The first treatment is speed: SE must be definitively treated with alacrity. The second conclusion is that the acute pathology causing SE is most likely to kill the patient, in both the short- and long term.

The Columbia data confirm the conclusion of the Veterans Affairs Cooperative Study of SE (Treiman DM, et al. *N Engl J Med.* 1998;339:792-798) as far as showing the increasing difficulty of stopping SE, the longer the condition is sustained. Although the duration of SE was not screened in the initial univariate analysis of factors correlated with RSE, when the Columbia investigators used the second ACD earlier than in the VA trial, the second-line agent was more effective. In addition, the fact that NCSE emerged as a significant risk factor for RSE implies a longer duration of SE, since NCSE is typically recognized much later than convulsive SE. The fact that SE continues to be a frequently fatal illness in the 21st century is disheartening. There can be no better model of neuronal excitoxicity than a condition that, by definition, involves unremitting cortical hyperexcitability. SE needs to be treated with the gravity and speed comparable to cardiopulmonary resuscitation. The critical topic for further studies is to attempt to formulate SE treatment algorithms comparable to those for Advanced Cardiac Life Support.

It has long been recognized that what causes SE is the main determinant of short-term survival. Logroscino et al have now shown that the same can be said for the influence of long-term mortality. Acute symptomatic SE (resulting from insults such as brain trauma, cerebrovascular disease, and CNS infection) has the worst outcome. Furthermore, SMR was not increased among patients with idiopathic or cryptogenic SE, implying that the SE per se does not alter long-term mortality. When neurologists are asked to judge the outcome of SE, these factors should guide discussions with medical colleagues and family members, but, as has just been argued, should not serve as an excuse for therapeutic nihilism. **—ANDY DEAN**

*Dr. Dean is Assistant Professor of Neurology and Neuroscience, Director of the Epilepsy Monitoring Unit, Department of Neurology, New York Presbyterian Hospital—Cornell Campus.*

# Sleep Apnea Syndrome: Insights into Neurocardiogenic Interactions

ABSTRACTS & COMMENTARY

**Sources:** Garrigue S, et al. *N Engl J Med.* 2002;346:404-412; Gottlieb DJ. *N Engl J Med.* 2002;346:444-445.

Sleep apnea syndrome (SAS) is a disorder with wide ranging physiological and social consequences. In the obstructive, "Pickwickian" type, obesity and a shortened, floppy upper airway result in severe snoring and impaired air flow. In the central type, there is a loss of medullary respiratory drive, resulting in prolonged periods of arrested respiratory effort. In either type, poor sleep hygiene results in frustrated bed partners, daytime sleepiness with impaired productivity, and even an increased incidence in vehicular accidents. Nocturnal hypoxia contributes to hypertension, right-sided heart failure, and increased cardiac mortality. Treatment with continuous positive airway pressure (CPAP) is effective, but often uncomfortable and always cumbersome.

The data of Garrigue and colleagues provide fascinating new insight into this disorder. They studied 15 patients with SAS, all of whom had a programmable dual chamber sequential pacemaker. These patients somewhat serendipitously had both conduction system (sinus node) disease requiring the pacemaker and SAS, 2 disorders not believed to be directly related. Although most of the patients had mild left ventricular dysfunction, heart failure was not thought to cause their noctural breathing problems.

Patients were roughly equally divided between obstructive and central types of SAS, which does rep-

resent a skewed population. More than 90% of SAS in the community have the obstructive type. Each patient was treated with atrial overdrive pacing at a rate of 15 beats per minute faster than their baseline. Episodes of apnea and hypopnea during polysomnography were measured according to strict accepted criteria. Obstructive or central events were distinguished by the presence or absence of diaphragmatic effort. The overall duration of sleep was not affected by treatment, indicating that any benefit of pacing was not merely a consequence of arousal. The hypopnea index (total number of episodes divided by the number of hours of sleep) was reduced with pacing from 9 ± 4 to 3 ± 3 ($P < 0.001$). For both apnea and hypopnea, the reduction was 28 ± 22 to 11 ± 14 ($P < 0.001$). Patients with both obstructive and central SAS benefited from treatment. Central apnea events, however, were more significantly reduced ($P < 0.007$) than those of an obstructive type ($P < 0.03$).

Garrigue et al speculate that atrial pacing maintains sympathetic activity and counteracts an excess of vagal tone in these patients. This vagolytic effect may then influence central respiratory drive. Such a reflex loop, they argue, which is known to exist for pulmonary afferents, may also be affected by sensory inputs from the heart.

### COMMENTARY

In the editorial accompanying Garrigue et al's report, Gottlieb further speculates on the possible mechanisms that may explain this apparently potent heart-lung-brain interaction. It is likely that cardiac vagal afferents directly affect respiration. These neurons form synapses in the nucleus of the tractus solitarius, which directly influences medullary respiratory control. It is more difficult, however, to explain how atrial pacing might effect obstructive SAS, a purely mechanical pharyngeal problem. As Gottlieb indicates, the activity of upper airway muscles, such as the genioglossus, appear to parallel diaphragmatic activity in a cyclical fashion. It is, therefore, possible that central factors guiding the respiratory process may have a powerful influence on neck muscle tone. It is also possible that the autonomic balance between sympathetic and parasympathetic activity may be important, as epinepherine has been shown to have an excitatory effect on respiratory neurons, including the pharyngeal muscles.

Although it is improbable that pacemaker insertion will become a standard therapy for SAS, these data provide a novel approach to a disorder with previously limited treatment. Perhaps these data can be generalized to patients without intrinsic cardiac disease. Interdisciplinary approaches to sleep medicine involving neurology, pulmonology, and cardiology will be needed to further explore this multisystem problem. **—ALAN Z. SEGAL**

# Myasthenia and Non-AchR Autoantibodies

ABSTRACT & COMMENTARY

**Source:** Romi F, et al. *Eur J Neurol.* 2002;9:55-61.

Among 43 patients with onset of generalized myasthenia gravis (MG) older than age 50, 21 were thymectomized and 22 nonthymectomized. Serum antimuscle antibodies were assessed annually, pre- and postoperatively, for 2-5 years to determine whether their presence was of prognostic value. By design, all patients were acetylcholine receptor (AChR) antibody-positive. Titin and ryanodine receptor (RyR) antibodies were measured by ELISA, the latter confirmed by Western blot. Chi-square and t-test provided statistical analysis.

Disease severity was comparable in all patients throughout the study period. Six antibody negative patients underwent remission, 4 with thymectomy alone, 2 with thymectomy plus immunosuppressive medication. Three non operated, titin-positive patients also experienced remission. No patient with both titin and RyR antibodies experienced remission. Three titin-positive thymectomized patients died from myasthenic respiratory complications in the 2 years following surgery and 3, 2 of whom were titin-positive, died from nonmyasthenic causes. Presence or absence of titin or RyR antibodies was not predictive of outcome to surgery nor of treatment necessary to control symptoms. However, all deaths were seen in titin-positive patients.

### COMMENTARY

Muscle antibodies are generally used to predict the presence of thymoma. RyR antibodies are present in 70% of thymoma cases, but also in 14% of late onset patients overall, and titin antibodies in 95% and 58%, respectively (Romi F, et al. *J Neurol.* 2000;247:369-375). Although ryanodine receptor and titin are intracellular proteins, their antibodies fix complement and correlate with disease severity (Romi F, et al. *J Neuroimmunol.* 2000;111:169-176; Romi F, et al. *Arch Neurol.* 2000;57:1596-1600). Their precise role in disease pathogenesis remains unclear.

RyR and titin antibodies are absent in seronegative

MG patients, defined as those with absent AchR antibodies (Romi F, et al. *J Neurol.* 2000;247:369-375). Nonetheless, these patients respond to immunosuppression and their immunoglobulin fraction transfers their weakness to mice, suggesting that their disease is also autoantibody mediated (Mossman S, et al. *Lancet.* 1986;1:116-119). Antibodies to muscle-specific receptor tyrosine kinase (MuSK, muscle specific kinase) have been demonstrated in 70% of these seronegative patients, but not in AchR positive patients. MuSK is one of a group of transmembrane receptors with tyrosine kinase activity, known as receptor tyrosine kinases (RTKs). It is skeletal muscle specific and highly localized to the motor endplate, suggesting a role in neuromuscular transmission (Valenzuela DM, et al. *Neuron.* 1995;15:573-584). Like RyR and titin, its role in pathogenesis remains to be elucidated (Palace J, et al. *Curr Opin Neurol.* 2001;14:583-589). **—MICHAEL RUBIN**

# Complex Regional Pain Syndrome

ABSTRACT & COMMENTARY

**Source:** Rho RH, et al. *Mayo Clin Proc.* 2002;77:174-180.

Reflex sympathetic dystrophy (RSD) as a syndrome is so broad that some feel it has lost its use as a clinical diagnosis. Neither reflex arcs nor the sympathetic nervous system are necessarily involved in RSD. Hence a new nosologic term, complex regional pain syndrome (CRPS), has been offered as a substitute. Two types of CRPS are proposed based on the presence (type II) or absence (type I) of an overt nerve lesion. Both types are otherwise clinically identical, with the development of a pain syndrome following an initial painful event. Pain, usually burning in character but also throbbing, aching, or shooting, allodynia (disproportionate pain to a non-noxious stimulus), hyperalgesia (disproportionate pain to a mildly noxious stimulus), and occasionally hyperpathia (disproportionate subjective response to noxious stimuli) are characteristic. Vasomotor and sudomotor abnormalities, including changes in color, temperature, and sweating, as well as hypertrophic or atrophic nails, increased or decreased hair growth, and skin atrophy, complete the clinical picture. Painful swollen joints, dystonia, and weakness are not uncommon.

No test is diagnostic for CRPS but vascular, electrodiagnostic, and radiographic studies must be normal (beyond any specific nerve injury) to exclude other etiologies. Examples of these include bone or soft tissue pathology, infection, vascular compression, or collagen vascular disease. Additional studies, including thermography, three-phase bone scintigraphy, sweat testing, and sympathetic blocks, are optional but may provide ancillary evidence of autonomic involvement.

Treatment centers on physical therapy as limb mobilization is the ultimate goal. Pain control is usually necessary and may require tricyclic antidepressants (amitriptyline, nortriptyline, doxepin), anticonvulsants (gabapentin), corticosteroids (early on and only short-term), or opioids if pain persists and interferes with therapy. Regional anesthetic sympathetic blocks (stellate or lumbar) may benefit patients with a sympathetic component to their CRPS but somatic blocks will be required if the former is ineffective. For recalcitrant cases, spinal cord stimulation or intrathecal analgesia with opioids or baclofen may be warranted.

## COMMENTARY

Problems dealing with RSD remain with CRPS. To evaluate RSD diagnostic criteria, as well as the effect of introducing the nosologic term CRPS, 20 years (1980- 2000) of randomized trials and clinical studies in RSD were reviewed using a PubMed search (van De Beek WJ, et al. *Neurology.* 2002;58:522-526). Case reports were excluded and only the last of multiple studies by van De Beek et al were included to avoid repetitive reporting bias. Seventy-three papers satisfied criteria for review. Among these, variance reigned. Disparate diagnostic criteria were used, some papers requiring from 2-6 mandatory features to make a diagnosis, others from 4-10 nonmandatory features, and yet others a combination of mandatory (1-5) and nonmandatory features (2-9). Although numerous sensory, autonomic, and motor features were criteria for diagnosis, in 30%, 20%, and 88% of studies, respectively, these were not required. Numerous alternative features were cited among diagnostic criteria but, again, these varied widely and included a precipitating factor (26%), radiographic changes (25%), trophic changes (21%), involvement of an area beyond the area of injury (11%), and contracture (10%). Of the 23 studies reported after the introduction of CRPS nosology (1995), equal variability of diagnostic criteria was evident. Only 10 studies used the term CRPS and, among these, at least 2 different sets of criteria were used. Two CRPS-entitled papers did

not use CRPS criteria. Two studies used previously defined CRPS criteria but had altered them slightly. RSD, CRPS, or causalgia remains a confusing morass and changing its name does not clear the inexactitude. A rose by any other name remains a rose, and wilted at that! —MICHAEL RUBIN

## Late Breakers

*Neurology Alert is pleased to introduce our new column "Late Breakers." In an effort to stay up to date, Neurology Alert will be including short reviews of current therapeutics in both early and pivotal stage development. Different from our usual format, the sources of our information for "Late Breakers" will be medical scientific meetings and company news releases.*

**Vagal nerve stimulation (VNS) fails in depression.** VNS has been a valuable adjunct to epilepsy treatment over the past 6 years. In an effort to expand its vagal nerve neuromodulatory franchise, Cyberonics Inc undertook a study of VNS in depression. Observational data from the epileptic population were notable for a mood enhancing response from VNS. A 60 nonepileptic depression patient pilot study (D-01) showed a 45% 1- year response rate. Response rate was defined as a ≥ 50% reduction in Hamilton Depression Rating Scale (HDRS). Overall remission in depression at 1 year was achieved in 27% of patients (HDRS ≤ 10). Benefit was proportional to the severity of the depression but no efficacy was seen in the most severe patients who had failed both ≥ 6 medications (Sackeim HA, et al. *Neuropsychopharmacology.* 2001;25:713-728). A pivotal randomized, double-blind, placebo-controlled crossover designed study (D-02) was undertaken in 235 patients. The 12-week acute data showed no statistical significant difference between placebo and the group receiving VNS. Unfortunately, the study protocol allowed too much discretion on the part of treating physicians and 52% of patients ended up receiving inadequate stimulation doses. Cyberonics maintains that the study failed rather than VNS for depression (Cyberonics news release). A new pivotal study is currently being planned. FDA supplemental approval is still possible. VNS is a well-tolerated mode of therapy and, as with epilepsy, given where polypharmacy is often required but poorly tolerated, it would a valuable addition to depression treatment.

**An Alzheimer vaccine trial is stopped**. Elan Corp and Wyeth-Ayerst Laboratories suspended all trials of the drug AN-1792 after 15 patients in the Phase IIa trial developed encephalitis. AN-1792 is a β-amyloid 42 amino acid vaccine that had already been tested safely in 360 patients during preclinical and Phase I trials. Data published in *Nature* 1999 showed that Aβ-42 injected into transgenic (PDAPP) mice could both prevent and reduce the formation of amyloid plaque. Details of the cases of these 15 patients have not yet been released (Elan news release).

**A new sleep drug with modified release efficacy**. Neurocrine Biosciences Inc announced positive results of NBI-34060 in a Phase II study of 47 patients with primary insomnia and sleep maintenance complaints. The primary end point was sleep efficiency, defined as total sleep time divided by 8 hours and measured objectively by polysomnography. NBI-34060 demonstrated 87-88.5% sleep efficiency compared to 84% in the placebo group ($P < 0.002$). An immediate release preparation is ion Phase III testing for sleep initiation. NBI-34060 is a specific GABA-A agonist, which is thought to be more potent than zolpidem (Ambien) and zaleplon (Sonata). The modified release formulation allows more flexibility in dosing particularly elderly patients with problems of sleep maintenance (Neurocrine news release). —JEFFREY REICH

## CME Questions

**17. In the United States, cases of arthropod-borne encephalitis have been caused by the all of the following *except*:**

a. LaCrosse virus.
b. rabies.
c. West Nile virus.
d. St. Louis encephalitis.

**18. All of the following statements regarding sleep apnea syndrome (SAS) are true *except*:**

a. SAS is a major cause of cardiovascular morbidity.
b. The obstructive type is more common than the central type.
c. Atrial pacing only benefits patients with central SAS.
d. Decreases in vagal tone may favorably affect respiratory drive.
e. Decreases in vagal tone may favorably affect pharyngeal muscle tone.

**In Future Issues:**

**Microsurgery for Lumbar Spinal Stenosis**