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Orexin and Human Narcolepsy: The Story Continues

ABSTRACTS & COMMENTARY

Sources: Scammell TE, et al. Narcolepsy and low CSF orexin (hypocretin) concentration after a diencephalic stroke. *Neurology.* 2001;56:1751-1753; Arii J, et al. A hypersomnolent girl with decreased CSF hypocretin level after removal of a hypothalamic tumor. *Neurology.* 2001;56:1775-1776; Dalal MA, et al. Normal plasma levels of orexin A (hypocretin-1) in narcoleptic patients. *Neurology.* 2001;56:1749-1751.

The past 2 years have been a gold rush in our understanding of the biological basis of narcolepsy. Progress in this area is summarized in recent editorials by Fred Plum (*Neurology Alert.* 2000;19:25-27) and Silber and Rye (*Neurology.* 2001; 56:1616-1618).

The peptides orexin A and orexin B (also termed hypocretin 1 and hypocretin 2) were discovered in the late 1990s (Sakurai et al. *Cell.* 1998;92:573-585). These peptides are largely distributed in specific nuclei of the hypothalamus and reticular activating system and were first described as possessing potent appetite-stimulating effects. The Silber and Rye editorial includes a diagram of the distribution of orexin-positive neurons.

In 1999, Lin and colleagues reported mutations in 1 of the 2 known hypocretin (Hcrt) receptors (Hcrt-2) in narcoleptic canines (*Cell.* 1999;98:409-412). Also, transgenic mice that bore mutant Hcrt receptors (Chemelli RM, et al. *Cell.* 1999;98:437-451) displayed cataplexy and altered REM sleep. Thus, as of 1999, it was clear that the orexin system played a crucial role in animal models of narcolepsy. It remained to be shown that this system had a similar role in human narcolepsy. Peyron and colleagues described mutations in Hcrt receptors in a case of early onset narcolepsy (*Nat Med.* 2000;6:991-997), but, unlike the dog, the majority of cases of human narcolepsy are not associated with mutations in Hcrt receptor. Both Peyron et al and Thannickal and colleagues (*Neuron.* 2000;27:469-474) found reduced numbers of orexin-containing neurons in human narcoleptic brains. Also, several groups have reported extremely low levels of orexin in the cerebrospinal fluid of narcoleptic patients. Thus, many cases of

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INSIDE

human narcolepsy can be explained by a selective degeneration of orexin-containing neurons.

Although most cases of human narcolepsy are idiopathic, this disorder has been rarely described in the context of brain injury. Scammell and colleagues recently reported a 23-year-old man with a history of craniopharyngioma who developed an extensive diencephalic stroke at age 18 immediately following tumor resection. Although he made a substantial neurological recovery, he subsequently developed all of the salient features of the narcoleptic tetrad (hypersomnolence, cataplexy, sleep paralysis, and hypnagogic hallucinations). Unlike most patients with idiopathic narcolepsy, this patient was negative for the HLA-DQB1*0602 allele. Scammell et al found an approximately 40% reduction in CSF orexin levels in this patient.

Arii and colleagues described another patient, a 16-year-old girl, who developed intermittent daytime somnolence approximately 4 months following resection of a hypothalamic Grade 2 pilocytic astrocytoma. Other components of the narcoleptic tetrad were not present in this patient. She was found to have an approximately 60% reduction in CSF orexin A (hypocretin-1). It is interesting that while Scammell et al and Arii et al found reductions in CSF orexin A in their patients with "secondary" narcolepsy, the reductions were not as profound as those reported in patients with primary, idiopathic narcolepsy.

If brain orexin deficiency is indeed central to most cases of human narcolepsy, it points the way to potential novel treatments. One potential treatment is orexin (a 115-amino acid peptide) itself. Kastin and Akerstrom showed that, in mice, orexin A could readily penetrate the blood brain barrier by simple diffusion (*J Pharmacol Exp Ther.* 1999;289:219-223). However, Dalal et al showed that, in humans, this must not be the case. They examined blood and CSF orexin A levels in 11 narcoleptic patients. CSF orexin A levels were markedly (> 90%) reduced as compared to normal control. Plasma orexin A levels were not statistically different from control. Thus, orexin A itself is unlikely to be of therapeutic value in human narcolepsy. However, it may be that bioactive fragments of orexin A may be of value.

COMMENTARY

In our view, the recent findings regarding the pathophysiology of narcolepsy represent one of the most exciting developments in neurology in the past few years. Neurologists should pay special attention to this field, as it is likely that developments which are likely to directly bear on patient care will rapidly emerge. One can predict that drugs modulating the orexin system will soon find their way into the therapeutic armamentarium. Indeed one may already have: there is some evidence that the analeptic drug Provigil (modafinil) activates orexin-containing neurons (Chemelli RM, et al. *Cell.* 1999;98:437-451) in experimental animals. **—rosario r. trifiletti**

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Anti-Hu Associated Paraneoplastic Encephalomyelitis

ABSTRACT & COMMENTARY

Source: Graus F, et al. Anti-hu-associated paraneoplastic encephalomyelitis: Analysis of 200 patients. *Brain.* 2001;124: 1138-1148.

Two european groups studying paraneoplastic syndromes, one headed by Frances Graus in Barcelona and the other by Jean Yves Delattre in Paris, studied 200 patients suffering from paraneoplastic encephalomyelitis associated with high titers (> 1:1000) of the anti-Hu (ANNA-1) paraneoplastic anti-

body. They reviewed the clinical findings to "identify patient-, tumor- and treatment-related characteristics associated with neurologic disability and survival." They found, as have previous investigators, that the paraneoplastic disease was devastating. Clinical symptoms of sensory neuropathy, cerebellar degeneration, cortical encephalitis, brainstem encephalitis, sensory motor neuropathy, and dysautonomia either singly or in combination marked the syndrome. The neurologic syndrome preceded identification of the tumor in 85% of the patients, and at diagnosis, more than half were disabled by the neurologic disorder. In those who died, 60% died a neurologic death. Only in 5% of patients were the clinical symptoms, usually those of sensory neuropathy, mild and indolent. The cancer was usually small-cell lung cancer and, in almost all instances, the associated cancer contained the Hu antigen. In those few that did not, sampling error may be responsible because at times only a minority of cells express the antigen.

Two factors of clinical importance loom large: The first is that the milder the clinical symptomatology, the longer the delay in finding the tumor. The second is that only tumor treatment appears to affect the course of the neurologic disease. Graus and colleagues were unable to adduce evidence that immunotherapy significantly ameliorated the neurologic syndrome.

COMMENTARY

This paper gives the neurologist enough information to identify the anti-Hu syndromes and manage them appropriately. The only difference between these European data and similar data from the United States is the percentage of women suffering from small-cell lung cancer. In Spain, women represent 15% of the small-cell lung cancer population and in France, 33%. At Memorial Sloan-Kettering Cancer Center, more than 50% of newly diagnosed small-cell lung cancers are in women. This is important because among patients with small-cell lung cancer, women are far more likely to develop a paraneoplastic syndrome than are men. With the data from this paper and serum for anti-Hu antibodies, the neurologist can make an early diagnosis of even mild sensory or sensorimotor neuropathy, cerebellar ataxia, or limbic encephalitis as having a paraneoplastic etiology. As this paper indicates, the only even partially effective treatment is early identification and eradication of the cancer, while the patient is still neurologically independent. (*Author's note: Graus et al kindly dedicated their paper to me. I am flattered, but I wish I had written it rather than inspired it.*) **—jerome b. posner**

Brain Stimulation Can Improve Tourette's Syndrome

ABSTRACT & COMMENTARY

Source: Babel TB, et al. Immediate and long-term outcome after infrathalamic and thalamic lesioning for intractable Tourette's syndrome. *J Neurol Neurosurg Psychiatry.* 2001; 70:666-671.

Motor and vocal tics are among the most common movement disorders, affecting as many as 5 in 10,000 people. Most patients with tics do not meet criteria for Tourette's syndrome, which requires motor and vocal tics to begin before age 21 and to be present for at least 1 year. Even among Tourette's patients, the vast majority do not require treatment for their tics. When tics interfere with scholastic or social activities, standard medications such as clonazepam, clonidine, guanfacine, and dopamine agonists usually provide adequate tic control. Even patients with more disabling tics can often be treated successfully with dopamine-depleting agents, such as reserpine or tetrabenazine, or even neuroleptic agents. The latter should be avoided if possible because of their unacceptable risk of inducing a tardive movement disorder.

It is rare for patients with severe Tourette's syndrome not to respond to conventional medications. These unusual patients have severe, debilitating tics that prevent them from participating in social interactions, including behaviors that may injure themselves or others. Termed "malignant Tourette's," they present a significant therapeutic challenge, and neurosurgical approaches including limbic leucotomy, cingulotomy, and thalamic lesioning have been attempted in desperation. Because these patients are so rare, most reports of these procedures describe single cases, preventing adequate evaluation of results.

In this paper, Babel and colleagues report their experience accumulated over 3 decades with 17 patients with malignant Tourette's treated with unilateral or bilateral thalamic surgery. They quantified the pre- and postoperative severity of motor and vocal tics by a simple scoring system. Nine patients underwent bilateral procedures, targeting the zona incerta, ventrolateral nucleus, and lamella medialis of the thalamus.

Babel et al documented a profound reduction in

motor and vocal tic scores ($P < 0.001$). These reductions in tic severity were maintained over time (an average of 7 years). Unilateral lesioning provided adequate control of tics. Immediate postoperative complications including dystonia, dysarthria, and cerebellar deficits were common, occurring in 11 patients. These disturbances did not improve in 3 patients, and in these cases they were a source of significant disability.

COMMENTARY

Malignant Tourette's syndrome is one of the most challenging hyperkinetic movement disorders. In the United States, few neurosurgical operations have been performed in these patients. This paper is of interest for several reasons. First, it documents that ablation of specific thalamic nuclei can improve motor and vocal tics, and that these effects can be long lasting. Second, it is not surprising that there was a high incidence of adverse events, and that a significant minority of these events were disabling. Many of the surgeries were performed prior to the availability of high-resolution magnetic resonance imaging, and it is now known that bilateral lesioning procedures have an unacceptable incidence of side effects of dysarthria and cognitive impairment.

In the future, most stereotactic surgeries will use deep brain stimulation instead of lesioning procedures. Deep brain stimulation is safer and also offers the opportunity to finetune stimulation parameters to obtain maximum benefit. Given the encouraging nature of Babel et al's results, a trial of deep brain stimulation of the thalamus for malignant Tourette's would appear warranted. **—steven frucht**

Update on Stroke Prevention: News from National Meetings—The WARSS and PROGRESS Trials

CONFERENCE COVERAGE

Source: Mohr JP for the warfarin-aspirin recurrent stroke study (WARSS) study group. Presented at the American Academy of Neurology, May 1999, Philadelphia, Pa.

The warss trial was designed to compare warfarin therapy with antiplatelet therapy (aspirin) in the prevention of recurrent stroke. The trial was a randomized, double-blind, multicenter trial of 2206 patients at 47 US centers. The trial had 4 substudies: PICSS, APASS, HAS, and GENESIS, examining issues such as the risk of stroke with patent foramen ovale (PFO) and antiphospholipid antibodies. Data from the substudies have not yet been presented.

The inclusion criterion for WARSS was an ischemic stroke within the prior 30 days. Patients with a cardioembolic source of stroke, such as atrial fibrillation (AF) or a symptomatic, operable carotid stenosis, were excluded. Patients were randomized to receive either aspirin (325 mg/d) or warfarin (INR 1.4-2.8) for at least 2 years. Adjustments of warfarin were based on either real or computer-generated INR values.

Among warfarin-treated patients, a mean INR 2.0-2.1 was sustained over 2-year follow-up. There were no statistical differences in the risk of recurrent stroke or in major hemorrhage. No statistical differences were found in subgroups defined by sex, race, or stroke subtype.

COMMENTARY

We eagerly await the upcoming formal publication of the WARSS data to provide further insight into this landmark study. These preliminary findings alone already portend a major decrease in the empiric use of warfarin post-stroke. The WARSS data, however, are open to at least 3 major criticisms that may still justify the use of coumadin by those who wish to use it.

1. The INR range chosen, 1.4-2.8, may have been too low. INRs in the range of 1.5-2.0 have been shown to be inadequate for stroke prevention in the setting of AF. It is possible that if all patients were maintained with INRs above 2.0, an advantage for warfarin may have been found.
2. The WARSS study was comprised of a large proportion of patients (> 50%), with lacunar disease. Since antiplatelet therapy rather than warfarin has traditionally been considered optimal for these small vessel lesions, inclusion of a these patients may have skewed the results toward aspirin. Data from the warfarin aspirin study of intracranial disease (WASID) comparing these therapies among patients with large vessel intracranial stenoses may yield different results.
3. Finally, while the WARSS study did not show an advantage for warfarin over aspirin, neither did it show a detriment. Under study conditions, with strict control of warfarin therapy, no increase in hemorrhage among warfarin patients was observed. If one is willing to accept the added inconvenience of warfarin therapy, its use remains justifiable based on the WARSS data.

J Chalmers for the Perindopril Protection Against Recurrent Stroke Study (PROGRESS). Presented at the 11th European Meeting on Hypertension, June 2001, Milan, Italy.

Hypertension is a well-recognized stroke risk factor. The immediate reduction of blood pressure in the post-stroke setting is, however, a matter of some controversy as perfusion may be augmented by higher blood pressures. Blood pressure control beyond the acute setting is a uniform goal in stroke survivors.

In the PROGRESS study, 6105 patients with a history of a stroke within the previous 5 years were randomized to a regimen of perindopril 4 mg along with indapamide 2.5 mg compared with placebo. All patients were treated with other antihypertensives as deemed necessary by their physicians along with medications such as aspirin and statin drugs.

The overall stroke risk was reduced by 28% in treated patients compared with placebo. The risk of fatal or disabling stroke was reduced by 38%. This benefit applied to both ischemic and hemorrhagic stroke. While patients with either hypertension or diabetes showed the most striking reduction (approximately 33%), a benefit of 22% was observed in patients without high blood pressure.

COMMENTARY

These data indicate that angiotensin converting enzyme (ACE) inhibitors have potent benefits in recurrent stroke prevention. This benefit applies irrespective of whether hypertension is actually present. These data parallel those of the heart outcomes prevention (HOPE) study (Yusuf S, et al. *N Engl J Med.* 2000;342:145-153) showing that the ACE inhibitor ramipril (Altace) provided marked reductions of both cardiac risk and stroke. The relative risk of stroke with ramipril treatment was 0.68 ($P < 0.001$) compared with placebo.

The accumulating data from studies such as PROGRESS and HOPE indicate that ACE inhibitors have vascular benefits extending far beyond blood pressure control. These effects may include anti-atherogenesis, arteriolar remodeling, endothelial cell modulation, platelet inhibition, and alterations in atrial naturetic peptide and other hormones. Most likely, this is a class effect applying to all ACE inhibitors. Perindopril is marketed in the United States under the trade name Aceon. The PROGRESS investigators specifically chose this drug for study as this agent is thought to maintain cerebral autoregulation and blood flow even in the setting of blood pressure reduction.

It is likely that future stroke prevention guidelines will include ACE inhibitor therapy regardless of whether hypertension is present. **—alan z. segal**

Cognitive Damage from SAH May be Less with Coiling Than Clipping

ABSTRACT & COMMENTARY

Source: Hadjivassiliou M, et al. Aneurysmal SAH. Cognitive outcome and structural damage after clipping or coiling. *Neurology.* 2001;56:1672-1677.

Hadjivassiliou and colleagues compared cognitive outcome and structural damage in patients with aneurysmal subarachnoid hemorrhage (SAH) treated in a nonrandomized manner either by surgical clipping (SC) or endovascular coiling (EC).

Forty case-matched pairs of patients with SAH who underwent SC or EC at 2 university hospitals in the United Kingdom during 1995 and 1996 were followed prospectively. Case matching was based on the following: World Federation of Neurologic Surgeons grade (Drake CG. *J Neurosurg.* 1998;68:985-986) on admission, age, location of aneurysm, and extent of SAH on CT scan. All patients underwent neuropsychological assessments at 1 year after treatment. Twenty-three case-matched pairs also underwent brain MRI at 1 year (*see Table*).

Table

MRI Results at 1 Year

Brain Lesion	Surgery (n = 23)	Coiling (n = 23)	P
Infarction	20	13	< 0.05
Surgical Damage (Focal Encephalomalacia)	19	0	< 0.001
White Matter Hyperintensities	15	19	NS

Both SC and EC groups were impaired in all cognitive domains when compared with age-matched healthy control subjects. The surgical group scored significantly worse than the endovascular group in 4 tests: the semantic fluency test, the vocabulary subtest of the WAIS-R (Weschsler D. *WAIS-R Manual.* New York: The Psychological Corporation, 1981), the complex figure recall test, and the extradimensional stage of the intradimensional/extradimensional shift test from the Cambridge Automated Neuropsychological Test Battery (Sahakian BJ, Owen AM. *JR Soc Med.* 1992;85:399-402).

On MRI, the prevalence of large vessel infarcts probably caused by vasospasm-induced ischemia was the same in both groups (SC, n = 8; EC, n = 9).

The surgical group, however, had a significantly larger number of patients with a single or multiple small infarcts (SC, n = 12; EC, n = 6) possibly due to compromise of adjacent perforating arteries during exposure and clipping of the aneurysm.

Hadjivassiliou et al conclude that although overall cognitive outcome after SAH primarily is determined by the characteristics of the initial hemorrhage, SC causes more structural damage and cognitive defects than EC.

COMMENTARY

The results of this study are sure to be embraced by interventional radiologists and patients' advocacy groups, just as they will be disputed by neurosurgeons. Nevertheless, the small number of patients enrolled and the major design flaws of the study (all patients having surgery were treated at Sheffield and all patients having endovascular procedures were at Oxford; all MRIs were read by the same neuroradiologist who could not be blinded because of the characteristic MRI appearances produced by the 2 procedures) should temper enthusiasms and prevent a firm clinical judgment at this time.

This interesting report is a foretaste of a larger, multicenter, randomized comparison of SC and EC—the International Subarachnoid Hemorrhage Trial that may revolutionize our approach to SAH. **—john j. caronna**

Flumazenil and Glucose PET Compared for Presurgical Delineation of Seizure Foci

ABSTRACT & COMMENTARY

Source: Juhasz C, et al. Relationship of flumazenil and glucose PET abnormalities to neocortical epilepsy surgery outcome. *Neurology.* 2001;56:1650-1658.

The success of surgery for intractable epilepsy depends upon the accurate presurgical delineation of the regions responsible for generating seizures. Juhasz and associates analyzed whether the extent of cortex showing 2-deoxy-2 [^{18}F] fluoro-D-glucose (FDG) or [^{11}C] flumazenil (FMZ) abnormalities correlated with the outcome of epilepsy surgery. They studied 15 young patients (8 girls and 7 boys, mean age 12 ± 7 years) with medically intractable partial epilepsy of neocortical origin who underwent cortical resection. Preoperative testing included brain MRI (normal in 9, abnormal in 6), EEG monitoring, and FDG and FMZ PET examinations. The extent of preoperative PET abnormalities was correlated with outcomes: seizure free (n = 8) or not seizure free (n = 7).

Large preoperative FMZ PET abnormalities were associated with poor outcome (r = 0.57; P = 0.025). Larger areas of nonresected cortex with preoperative FMZ PET abnormalities in the lobe of seizure onset also were associated with worse outcomes in the whole group (r = 0.66; P = 0.007), in patients with extratemporal resection (r = 0.73; P = 0.007) and in those with no lesion on MRI (r = 0.06; P = 0.049). Patients who were seizure free had smaller nonresected cortex with FMZ PET abnormalities than those who continued to have seizures (P = 0.022). No significant correlations were found between nonresected FDG PET abnormalities and surgical outcome.

COMMENTARY

This study showed first that better outcomes of neocortical epilepsy surgery can be achieved when preoperative cortical FMZ PET abnormalities are smaller and when the bulk of the cortex with FMZ PET abnormalities in the lobe of the epileptic focus is resected. This was true both for patients with nonlesional and extratemporal epilepsy.

The second finding was that the size of nonresected FDG PET abnormalities was not a predictor of outcome of neocortical epilepsy surgery. Other studies have shown that the degree of temporal lobe hypometabolism measured by FDG PET is a strong predictor of outcome after temporal lobectomy (Radthe RA, et al. *Neurology.* 1993;43:1088-1092; Manno EM, et al. *Neurology.* 1994;44:2331-2336; Theodore WH, et al. *Epilepsia.* 1997;38:81-86). In the present study, neocortical FDG PET abnormalities generally were larger and occasionally were localized to different cortical areas than the FMZ PET abnormalities. Although FDG PET successfully indicated some abnormality in the lobe of seizure onset, the size of the region of glucose hypometabolism did not reflect the exact anatomic location or size of the epileptogenic cortex.

FMZ PET seems to be particularly useful in defining the epileptogenic region in patients with nonfocal EEG results and large FDG PET abnormalities. **—john j. caronna**

Brief Alerts

Early Diagnosis of Guillain-Barré Syndrome

Source: Gordon PH, Wilbourn AJ. Early electrodiagnostic findings in Guillain-Barré syndrome. *Arch Neurol.* 2001;58:913-917.

Objective laboratory evidence is of significant benefit in supporting a clinical impression of Guillain-Barré syndrome (GBS). Unfortunately, cytoalbumino-

genic dissociation, the hallmark of GBS, is normal in 34% within the first week. Alternative avenues to support the diagnosis include nerve conduction studies (NCS) but such abnormalities are often similarly belated. When is the soonest GBS may be diagnosed electrodiagnostically and what are the earliest NCS abnormalities found?

A retrospective review of discharge diagnoses from the Cleveland Clinic in Cleveland, Ohio, covering the past 16 years revealed 31 GBS patients who underwent NCS in the first week of symptom onset. The more frequent abnormalities are tabulated in the Table below.

Table

Frequent Abnormalities of GBS

Abnormality	Frequency (%)
H reflex absent	30/31 (97)
F wave (arm) absent	17/31 (55)
F wave (leg) absent	19/31 (61)
Motor amplitude low	22/31 (71)
Motor amplitude low > 1 nerve	19/31 (61)
Prolonged distal motor latency	19/31 (61)
Slow conduction velocity	16/31 (52)
Temporal dispersion	18/31 (58)
Sensory response absent (arm)	12/31 (39)
Absent sural sensory response	5/31 (16)

Late responses (H reflex and F waves) are the earliest and most sensitive NCS abnormalities in GBS but, even with multiple nerve testing, diagnosis is possible in only half, and not before day 5.

COMMENTARY

Late response abnormalities, when occurring early, underscore the vulnerability of proximal nerve segments to demyelination, while the distal portions more commonly studied remain normal (*Ann Neurol.* 1978;35:344-350). Early diagnosis remains challenging. Up to 20% of GBS patients will demonstrate normal NCS during the first 2 weeks (Eisen A, Humphreys P. *Arch Neurol.* 1974;30:438-443; *Arch Neurol.* 1975;32:524-529). **—michael rubin**

Predicting Respiratory Compromise in GBS

Sources: Lawn ND, et al. Anticipating mechanical ventilation in Guillain-Barré syndrome. *Arch Neurol.* 2001;58:893-898. Hahn AF. The challenge of respiratory dysfunction in Guillain-Barré syndrome. *Arch Neurol.* 2001;58:871-872.

Firm guidelines exist for intubating guillain-Barré syndrome (GBS) patients. When vital capacity drops below 15 mL/kg, arterial Po_2 below 70%, or in the presence of severe bulbar weakness or respiratory fatigue, mechanical ventilation is imperative. Can one predict which patients will arrive at this point and thus warrant precautionary intensive care unit (ICU) observation?

Sixty severe GBS patients requiring mechanical ventilation were compared to 54 severe nonventilated GBS patients to determine clinical and electrophysiologic predictors of respiratory failure. No clinical feature foretold the pattern of respiratory decline, including age, gender, preceding gastrointestinal illness, arm paralysis, lung disease, cerebrospinal fluid findings, nerve conduction study abnormalities including inexcitable nerves prior to peak disability, or lack of treatment with immune globulin or plasmapheresis. Bulbar and autonomic dysfunction, peak disability within 7 days of onset of neuropathic symptoms, and bilateral facial paresis was significantly associated with the need for ventilatory support. Importantly, vital capacity less than 20 mL/kg, maximum inspiratory and expiratory pressures less than 30 cm H_2O and 40 cm H_2O, respectively, or a > 30% decrease in any of these measurements, predicted progression to ventilatory failure. GBS patients should be closely monitored for these parameters and when present, timely transfer to the ICU is warranted with an eye toward elective intubation as needed.

COMMENTARY

Dubbed the 20/30/40 rule, these guidelines add an easily retained and important dimension to the care of GBS patients. Evidence of bulbar dysfunction and aspiration also mandates ICU transfer and intubation. **—michael rubin**

Carpal Tunnel Syndrome

Sources: Padua L, et al. Multiperspective follow-up of untreated carpal tunnel syndrome: A multicenter study. *Neurology.* 2001;56:1459-1466. Wong SM, et al. Local vs systemic corticosteroids in the treatment of carpal tunnel syndrome. *Neurology.* 2001;56:1565-1567. Stevens JC, et al. The frequency of carpal tunnel syndrome in computer users at a medical facility. *Neurology.* 2001;56:1568-1570.

First described by pierre marie and charles Foix in 1913 (*Rev Neurol.* 1913;26:647-649), carpal tunnel syndrome (CTS) is the most common abnormality seen in electromyography laboratories across the United States. Multiple treatment modali-

ties exist, including steroids, orally or by injection, the latter first reported by Phalen and Kendrick in 1957 (*JAMA*. 1957;164:524-530). How well do they compare?

Among 60 CTS patients prospectively enrolled, 30 were randomized to local injection of 15 mg methylprednisolone acetate vs. placebo, and 30 to oral prednisolone 25 mg daily for 10 days vs. placebo. Both active treatment groups significantly improved their global symptom score (GSS) at 2 and 8 weeks, but only steroid injection showed significant GSS improvement at 12 weeks (Herskovitz S, et al. *Neurology.* 1995;45: 1923-1925). No significant side effects were seen in either group. Steroids work, and a single local injection is better than an oral 10-day course.

Is CTS associated with computer use? Certainly, if you ask many litigation lawyers. However, among 257 of 314 employees identified as frequent computer users who participated in a survey, 181 (70%) reported no CTS symptomatology. Of the remaining 76, 70 were interviewed. Twenty-seven were classified as CTS, 18 possible, and 9 definite. Overall, 10.5% met clinical criteria for CTS which was confirmed by nerve conduction studies in 3.5%. These percentages are comparable to those of the general population. Will this ease the dockets? Wish that it were so!

Lastly, under "why did this merit publication as a full article, and with CME credit to boot," we learn that CTS improves spontaneously. Among 274 hands with idiopathic CTS, spontaneous resolution was associated, surprisingly, with more severe initial symptomatology, as well as younger age, and short duration of symptoms. Milder initial impairment, bilateral baseline symptoms, and positive Phalen sign predicted a poor prognosis. The findings are interesting but this report will not change treatment practices for CTS as they present to your office. It will be a boon to disability lawyers and their clients. A letter to the editor would have sufficed. **—michael rubin**

CME Questions

4. In narcoleptics:
a. orexin receptor mutations are commonly found.
b. plasma orexin levels are low.
c. significant reductions in CSF orexin A may be found in both secondary and idiopathic narcolepsy.
d. improvement can be expected with orally administered orexin A.

5. A comparison of surgical clipping (SC) with endovascular coiling (EC) in patients with ruptured aneurysms found all of the following *except*:
a. both treatment groups were cognitively impaired.
b. the SC group had more cognitive impairment than the EC group.
c. the EC group had more cognitive impairment than the SC group.
d. the SC group had more small infarcts.
e. the prevalence of large vasospasm-caused infarcts was the same in both groups.

6. All of the following are prognostic factors in the outcome of epilepsy surgery *except*:
a. the extent of preoperative FMZ PET abnormalities.
b. the extent of nonresected cortex with preoperative FMZ PET abnormalities.
c. the extent of preoperative FDG PET abnormalities in temporal lobe.
d. the extent of FDG PET abnormalities in cortex remote from the area resected.
e. the extent of preoperative FMZ PET abnormalities in patients with negative MRIs.

7. Carpal tunnel syndrome (CTS):
a. is associated with computer use.
b. responds identically to steroids, given either orally or by local injection.
c. usually requires surgery, even for mild cases.
d. is more likely to further worsen when symptoms are severe, rather than mild, at presentation.
e. None of the above

8. When monitoring Guillain-Barré syndrome patients for possible respiratory failure, which of the following indicate the need for ICU monitoring for possible impending respiratory failure?
a. Vital capacity > 20 mL/kg
b. Maximum inspiratory pressure < 30 cm H_2O
c. Maximum expiratory pressure < 40 cm H_2O
d. A > 30% decrease in vital capacity, maximum inspiratory pressure, or maximum expiratory pressure
e. All of the above

9. What are the most frequent early NCS abnormalities found in Guillain-Barré syndrome (GBS)?
a. Late response (F wave and H reflex) abnormalities
b. Decreased sensory response amplitudes
c. Prolonged distal motor latencies
d. Temporal dispersion
e. Slowed conduction velocities

10. Babel et al found that ablation of specific thalamic nuclei can improve motor and vocal tics in malignant Tourette's syndrome.
a. True
b. False

In Future Issues:

Language Regression in Children: An Ominous Sign