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Neurology [ALERT®]

Evidence-based summaries of the latest clinical neurology research

ABSTRACT & COMMENTARY

To Sleep, Perchance to Clear Our Beta-Amyloid

By Alan Z. Segal, MD

Associate Professor of Clinical Neurology, Weill Cornell Medical College

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

SYNOPSIS: Both animal studies and human data suggest that A-beta 42 amyloid is cleared from the brain during sleep, and that sleep deprivation may be a risk factor for the development of Alzheimer's disease.

SOURCE: Ooms S, et al. Effect of 1 night of total sleep deprivation on cerebrospinal fluid B-amyloid 42 in healthy middle-aged men: A randomized clinical trial. *JAMA Neurol* 2014;71:971-977.

Theories of "why we sleep" date back to the Greek and Roman philosophers, who believed that dreams were of divine origin. Kierkegaard called sleep the "highest accomplishment of genius." In more modern times, adequate, effective sleep is well known to be a major contributor to daytime alertness/vigilance, concentration, and declarative memory. Cognitive performance may be impaired by acute, total sleep deprivation for 1-2 nights or a more moderate, chronic lack of sleep (< 6 hours per night for 14 or more days).

More recent data suggest that these effects may not be transient, but rather cumulative over time and contribute to long-term cognitive decline and dementia, specifically Alzheimer's disease (AD). Sleep has been shown to have a direct influence on the quantity of beta-amyloid (Aß) deposition in the brain as measured by PET scanning (Amyvid or Pittsburgh Compound B). Carriers of the ApoE4 genotype, who are at increased risk for developing AD, are even more prone to the disease if they suffer from poor quality sleep. Recently, increased neural activity in wakefulness has been shown to correlate with an augmentation of A-beta 42 production, with increased A-beta clearance during sleep. Groundbreaking data from the University of Rochester, recently reported in *Science*,[1] has shown that in sleeping mice a process known as the

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"glymphatic" system increases the quantity of cerebrospinal fluid (CSF) "flushing" through the brain. Using a process of CSF "iontophoresis," this research showed that with an expansion of the volume of the interstitial space during sleep (a contraction of neurons), there was a 60% increase in CSF passage into the venous system. This system, likened to a "disposal system for the brain," is believed to allow for more effective clearance of toxins, specifically beta-amyloid.

In the current study, 26 middle-aged men were randomized equally to a normal night's sleep compared with a full 24 hours awake. CSF was sequentially collected through a lumbar catheter. Subjects who slept showed a statistically significant 6% reduction in A-beta 42, where subjects who stayed awake did not demonstrate this decrease. This "morning effect" of decreased CSF A-beta 42 following sleep had previously been demonstrated in both rodents and humans but this study uniquely proved that lack of sleep would abort this effect. Not surprisingly, this difference in A-beta 42 levels did not apply to secondary markers studied such as A-beta 40 (which are a lesser contributor to plaque production) and tau (which is typically increased in much later phases of AD).

Measurement of sleep may be most accurately accomplished in a sleep laboratory with polysomnography, as was done here. Alternatively, sleep may be reported retrospectively, with nightly sleep logs or with measurement of actigraphic muscle activity or accelerometers such as the hugely popular "Fit-bit." Interestingly, the subjects studied here got poorer sleep than they might have at home. Prior to the study, these subjects all scored > 5 on the Pittsburgh Sleep Quality Index, evidence of normal sleep integrity. Studied in the lab, these individuals had a WASO (wake after sleep onset) of 92 minutes (normal < 30 min) and a sleep efficiency (total sleep time/total time in bed) of 77% (normal > 85%). It is possible that the favorable effects on A-beta 42 may have even been more pronounced with a better night's sleep?

■ COMMENTARY

These data, in combination with those in the *Science* report, lend credence to the theory that toxins such as A-beta 42 accumulate while we are awake and are cleared when we are asleep. This work lends biochemical support to the many behavioral studies (population-based cohorts) that have shown that short sleep times as well as sleep-onset and sleep-maintenance insomnia contribute to both immediate and long-term cognitive sequela. Obstructive sleep apnea, which has been clearly shown to contribute to dementia, is not only damaging due to hypoxia but also due to disruption of sleep integrity. Sedative-hypnotic drugs such as zolpidem or benzodiazepines may increase sleep time but impair slow-delta wave (Stage III) sleep and may have long-term deleterious cognitive effects. As we age, our ability to initiate and maintain quality sleep wanes even in the best of circumstances, but this should not stop us from trying to get as much as possible. ■

REFERENCE

1. Xie L, et al. Sleep drives metabolite clearance from the adult brain. *Science* 2013;342:373-377.

ABSTRACT & COMMENTARY

Chemotherapy-Induced Neuropathy in Pediatrics

By Michael Rubin, MD

Professor of Clinical Neurology, Weill Cornell Medical College

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

SYNOPSIS: Chemotherapy-induced peripheral neuropathy is common in children treated for a variety of cancers, but the long-term prognosis for recovery is excellent.

SOURCE: Purser MJ, et al. Chemotherapy-induced peripheral neuropathy among paediatric oncology patients. *Can J Neurol* Sci 2014;41:442-447.

With improvement in cancer survival, long-term neurotoxicity is becoming an ever-increasing concern. Varying with the chemotherapeutic agent, drug dose, duration of exposure, and diagnostic criteria, the incidence of chemotherapy-induced peripheral neuropathy (CIPN) varies from 30-75% in adults. What is its incidence in children?

Between 2001-2011, 274 pediatric patients treated at Children's Hospital of Eastern Ontario for acute lymphoblastic leukemia (ALL), lymphoma, brain tumor, or Wilms' tumor were considered for this retrospective cohort study. Inclusion criteria were age < 18 years, pathologic or imaging confirmation of diagnosis, and treatment with chemotherapy, with exclusion criteria encompassing lack of treatment with chemotherapy, alternative cause other than neuropathy found for symptoms, or incomplete medical records. Charts were reviewed to determine the presence of sensory complaints, ataxia, or weakness, and electrodiagnostic studies and imaging studies were examined. CIPN was diagnosed if sensory or motor difficulties developed during chemotherapy that the treating neurologist or oncologist believed to be due to peripheral neuropathy. If a central cause could explain the symptoms, they were not diagnosed as CIPN. Statistical analysis was performed using the unpaired, two-tailed student t-test, with $P \leq 0.05$ considered significant.

Among the 274 patients, 22 did not meet inclusion criteria and were excluded from further study. Among the remaining 252 eligible patients, the average age of cancer diagnosis was 6.7 years for ALL, 10.8 years for lymphoma, 6.4 years for brain tumor, and 3.5 years for Wilms' tumor. None had a personal or family history of hereditary neuropathy. CIPN was diagnosed in 18.3% (46/252) of the entire cohort, 18.8% of ALL, 9.4% of lymphoma, 23.7% of brain tumors, and 17.9% of Wilms' tumor. Using the U.S. Department of Health and Human Services Common Terminology Criteria for Adverse Events (CTCAE), 78% (36/46) of CIPN patients experienced grade 2 toxicity, implying moderate symptoms affecting activities of daily living. CIPN most often presented with either purely motor (46%) or sensorimotor (39%) symptoms, with 15% experiencing sensory symptoms alone. Motor symptoms included foot drop, clumsy ataxic gait, and impaired fine motor movements, while sensory symptoms included limb paresthesiae and pain. Among the eight patients who underwent confirmatory electrodiagnostic studies, all but one had an axonal neuropathy, with small fiber neuropathy suspected in the outlier. Although 62 children underwent radiotherapy, none had asymmetrical symptoms or fasciculations suggestive of radiation nerve injury. Recovery from CIPN was excellent among surviving patients, with 93% (41/46) showing no clinical deficits on last follow up, an average of 56 months following CIPN diagnosis.

■ COMMENTARY

No effective agents convincingly prevent CIPN, including alpha-lipoic acid, calcium/magnesium, glutathione, recombinant human leucocyte inhibitory factor, or vitamin E. Administering bortezomib (Velcade, used to treat multiple myeloma and mantle cell lymphoma) weekly rather than twice weekly, and subcutaneously rather than intravenously, will decrease, but not prevent, the incidence of CIPN and lessen its severity. Once established, pain associated with CIPN may be treated with duloxetine, the only agent shown in a double-blind, crossover trial to be effective, though the magnitude of benefit was modest. Agents used for neuropathic pain, including antiepileptic and tricyclic antidepressant medication, may be offered, but none have proven superior to placebo in CIPN clinical trials. Topical menthol, applied twice daily, has reportedly provided relief, but only in individual case reports. Amitriptyline, baclofen, and ketamine, compounded in a gel, were compared to placebo in a randomized North Central Cancer Treatment Group trial, and demonstrated significant motor subscale improvement, with statistically non-significant improvement in sensory neuropathy. Hence, it requires more study before it can be recommended. ■

ABSTRACT & COMMENTARY

Neuropsychological Assessment Reduces False Positives in Mild Cognitive Impairment

By Lisa D. Ravdin, PhD, ABPP

Associate Professor of Neuropsychology, Weill Cornell Medical College

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

SYNOPSIS: Traditional comprehensive neuropsychological testing has greater reliability, sensitivity, and specificity than bedside screening tests in the accurate diagnosis of mild cognitive impairment.

SOURCE: Klekociuk SZ, et al. Reducing false positive diagnoses in mild cognitive impairment: The importance of comprehensive neuropsychological assessment. *Europ J Neurol* 2014;21:1330-1336.

Mild cognitive impairment (MCI) is a term initially used to describe reduced memory functioning as an intermediary stage between age-related memory changes and dementia. The classification of MCI has since been expanded to include non-memory cognitive changes, as well as various subtypes of presentation (i.e., single or multiple affected cognitive domains). Given the high level of function of those with MCI, neuropsychological assessment is better suited than bedside cognitive screening in terms of detection, distinguishing subtypes, and objectively measuring patterns of progression.

The aim of this study was to assess the ability of neuropsychological measures to predict true positive classification of MCI over time. Participants were examined at a baseline screening plus two additional time points approximately 9 months (± 3 months) and 11 months (± 1 month) later. Screening consisted of a battery of tests that differed in actual measures but tapped the same cognitive domains assessed at the follow-up visits. One hundred eighteen community-residing subjects had data from the three time points and were included in the analyses. MCI was defined as > 1.28 standard deviation (< 10th percentile) below the mean on one or more cognitive measures. Stability classifications were based on consistency of classifications across visits; subjects who met MCI criteria at all three time points or those who were initially unimpaired on screening but met criteria for MCI at visit 1 and 2 were given the stability classification of MCI. Those identified as MCI at screening, but performed within normal limits on subsequent visits, were classified as unimpaired, as were those who continually were unimpaired at all three test visits. Discriminant function analyses revealed test scores from multiple cognitive domains predicted group outcome, accounting for 83.9% of cases. A false-positive rate of 5.93% using this model was consistently lower than false-positive rates of misdiagnosis based on diagnostic criteria alone (23.73%).

The data suggest that memory testing in isolation is insufficient for recognizing MCI, and that reduced scores on tests of other higher order cognitive processes (i.e., executive function) enhance the ability to identify true positive cases. In fact, the strongest predictor of stability of MCI was a non-memory measure, Rapid Visual Processing, a formal test of sustained attention. Unlike other studies, the analyses did not examine different effects for those with single vs multiple domain MCI. Stability may vary depending on subtype, and others have shown the number of domains affected predicts outcome. Age is yet another factor not examined here that has been shown in other studies to be associated with lower diagnostic stability of MCI classification.

■ COMMENTARY

MCI is becoming a household word for educated medical consumers, but in practice there are discrepancies in the operational definition, with some clinicians considering the term to be virtually synonymous with early-stage dementia and others recognizing it as a risk factor for Alzheimer's disease (AD) or generalized cognitive decline. There are likely a variety of etiologies of MCI, some of which may not necessarily be progressive in nature. The concept of "MCI due to AD" has been used to describe individuals with cognitive changes that are most likely secondary to pathophysiological processes associated with AD, and this group can theoretically be differentiated from those with a more static cognitive disturbance or the considerable number of cases that revert to normal. In practice, classification errors can arise due to clinical biases or insufficient methodology. "One test" methods have been criticized for their limited ability to identify cognitive decline, particularly in cases of subtle impairment, as is the case in MCI. The same can be said for bedside mental status screening that can show a ceiling effect and lack sensitivity in the high-functioning MCI patient. These data highlight that formal neuropsychological assessment is associated with fewer false-positive classifications of MCI. Of note, interpretation of scores on cognitive measures should account for the effects of age, education, and cultural factors on test performance. Efforts aimed at improving recognition and classification of MCI can have a significant impact on clinical care as well as better identification of appropriate individuals for future prevention trials. ■

ABSTRACT & COMMENTARY

New Diagnostic Methods for Creutzfeldt-Jakob Disease

By Joseph E. Safdieh, MD

Assistant Professor of Neurology, Weill Cornell Medical College

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

SYNOPSIS: Novel noninvasive diagnostic tests for Creutzfeldt-Jakob disease (CJD; nasal brushings) and variant CJD (urinary prion proteins) are reported to be highly sensitive and specific in two recent studies.

SOURCES: Orru' CD, et al. A test for Creutzfeldt-Jakob disease using nasal brushings. *N Engl J Med* 2014;371:519-529.
Moda F, et al. Prions in the urine of patients with variant Creutzfeldt-Jakob disease. *N Engl J Med* 2014;371:530-539.
Masters CL. Shaken, not sonicated? Editorial. *N Engl J Med* 2014;371:571-572.

Prion diseases are rare and uniformly fatal neurologic conditions. They are caused by propagation of misfolded proteins from the normal form to the pathogenic form. Prion diseases in humans include Creutzfeld-Jakob disease (CJD), variant CJD, fatal familial insomnia, and Gerstmann–Sträussler–Scheinker syndrome. Prion diseases are unique among all medical disorders in that they can be inherited or transmitted. Variant CJD is caused by exposure to the bovine spongiform encephalopathy prion and is acquired by eating infected meat. Patients are suspected to have CJD when they present with a rapidly progressive dementia, associated lumbar puncture characteristics (14-3-3 protein), and associated MRI changes (cortical ribbon and thalamic/basal ganglia hyperintensities on diffusion weighted imaging). However, none of these tests provide enough sensitivity and specificity to firmly establish the diagnosis, often necessitating a brain biopsy. In this set of studies, the authors propose novel, non-invasive methods to diagnose CJD and variant CJD.

Orru et al looked at a novel method of detecting abnormal prion protein via a method called real-time quaking-induced conversion (RT-QUIC) in nasal brushings of patients with and without CJD. RT-QUIC is performed by mixing recombinant prion protein with small amounts of human pathogenic prion protein resulting in the formation of amyloid fibrils that can be detected by Thioflavin T staining. In a prior study, CSF RT-QUIC was found to be 80-90% sensitive in the diagnosis of CJD. In this study, the authors evaluated the sensitivity and specificity of RT-QUIC testing of nasal brushings. The results demonstrated that the RT-QUIC was positive in 30 of 31 cases of confirmed CJD and was negative in all 43 non-CJD patients. Calculated sensitivity was 97% and specificity was 100%. The authors also performed CSF RT-QUIC on the same group of samples and determined a much lower sensitivity of 77%, with the same 100% specificity. Nasal brushings had much higher levels of the abnormal prion protein than CSF.

Moda et al looked at a novel method of detecting abnormal prion protein called PMCA (protein misfolding cyclic amplification) in the urine of patients with and without variant CJD. PMCA is performed by mixing the pellet from centrifuged urine with a suspension of brain specimen from transgenic mice expressing human prior protein. The authors tested urine from patients with variant CJD, sporadic CJD and other non-prion neurologic illnesses as well as healthy controls. The results demonstrated that via PMCA, 13 of 14 patients with variant CJD had detectable abnormal prion in the urine and none of the 224 patients (including those with sporadic and genetic prion diseases) were positive. Calculated sensitivity was 92.9% and specificity 100%.

■ COMMENTARY

Both of these studies are extremely important additions to the medical diagnostic literature and move us a step closer to making the diagnosis of CJD and variant CJD without the need to perform brain biopsy, and potentially without the need to perform lumbar puncture. In fact, for sporadic CJD the sensitivity of RT-QUIC is much higher in the nasal brushings than CSF, suggesting that testing nasal brushings may actually be preferred over CSF. In the setting of an appropriate clinical picture and a compatible MRI, a positive RT-QUIC test in nasal brushings will likely have a very positive predictive value, although it is not fully sensitive so a negative test may not exclude the disease. It also seems that a positive test for urine PMCA in variant CJD is likely to have a high positive predictive value, but again a negative test does not fully exclude the disease. More work needs to be done to confirm these findings, and more samples tested will likely tighten up the confidence intervals for specificity, but these studies are very promising and raise the likelihood that there will be a simple non-invasive test for diagnosing CJD or variant CJD in the near future. ■

ABSTRACT & COMMENTARY

Role of Neurologists and Diagnostic Tests in the Management of DSP

By Louise M. Klebanoff, MD

Associate Professor of Clinical Neurology, Weill Cornell Medical College

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

SYNOPSIS: Using the clinical history and simple, inexpensive laboratory tests, community-based outpatient neurologists were able to determine the cause of distal symmetric polyneuropathy in three-fourths of patients presenting with typical symptoms. More costly diagnostic testing, including electrophysiological testing and magnetic resonance imaging, did not add to the accuracy of diagnosis or management of this patient population.

SOURCE: Callaghan BC, et al. Role of neurologists and diagnostic tests of the management of distal symmetric polyneuropathy. *JAMA Neurol* 2014:71:1143-1149.

Peripheral neuropathy is the most common disorder of the peripheral nervous system, with a prevalence of 2-7% in the entire population and a prevalence of > 10% in the elderly. Disorders of the peripheral nervous system account for 1.5 million visits to neurologists annually. Diagnostic testing of these disorders by outpatient neurologists can be costly. The cost for diagnostic testing is $375 million each year, $205 million (57%) for electrodiagnostic tests and $135 million (38%) for magnetic resonance imaging (MRI). For distal symmetric polyneuropathy (DSP), the most common subtype of peripheral neuropathy, current evidence supports several routine and inexpensive diagnostic laboratory studies including fasting glucose, vitamin B12 level, serum protein electrophoresis, and glucose tolerance tests for the initial evaluation. Few data are available to assess the value of more expensive diagnostic testing such as electrophysiological testing and MRI in the assessment of patients with DSP. In addition, the value of the community neurologist in the diagnostic testing and management of patients with DSP is unknown.

[…electrophysiological testing should be reserved for patients with atypical presentations, such as concern for inherited, vasculitic, or demyelinating neruopathy.]

The authors performed a retrospective cohort study using a validated case-capture method to identify all patients with a new diagnosis of DSP treated by community neurologists is Nueces County, Texas, from April 1, 2010 through March 31, 2011. Patients were required to meet the Toronto Diabetic Neuropathy Expert Group consensus panel definition of probable neuropathy, which is two or more of the following criteria: neuropathic symptoms (self-report of pain, numbness, and/or tingling in the feet and/or legs), decreased distal sensation on neurological examination, or decreased or absent ankle jerks. Patients who were seen only in the hospital, who only underwent electrophysiological testing, or who were previously diagnosed as having neuropathy by a neurologist were excluded. Medical records were extracted by a trained research coordinator using the entire outpatient medical record. The suspected causes of the neuropathy, as identified by the neurologist at the initial evaluation and at the last follow-up evaluation, were also documented. All management changes were also recorded.

The authors screened the medical records of 4890 patients, identified 831 by the initial screening criteria, and excluded 86 due the previously defined exclusionary criteria and another 287 who did not meet the Toronto consensus for probably DSP, leaving 458 patients for further analysis. The mean (SD) age of the patients was 65.8 (12.9) years, and 258 (56.3%) were women. The mean duration of follow-up was 435.3 (44.1) days over 2.4 (1.6) visits. Neurologists ordered electrodiagnostic testing in 353 patients (77.1%) and MRI of the neuroaxis in 65 (14.2%). In terms of the Academy of Neurology recommended tests, measurement of vitamin B12 level was ordered in 177 patients (38.6%), fasting blood glucose in 56 (12.2%), serum protein electrophoresis in 127 patients (27.7%), and glucose tolerance tests in 144 patients (31.4%).

Prior to diagnostic testing, neurologists were able to determine the cause of DSP in 291 patients (63.5%), with the most common cause being diabetes (233 patients) followed by thyroid condition (31 patients), alcohol (14 patients), chemotherapy (9 patients), and vitamin B 12 deficiency (8 patients). Before diagnostic testing, 167 patients (36.5%) had no clearly defined cause for their DSP; with diagnostic testing a new cause was determined in 45 patients. In total, neurologists discovered a new cause of DSP in 71 patients, 28 with prediabetes, 20 with vitamin B12 deficiency, eight with diabetes, and eight with thyroid disorders. Neurologists determined a new cause for DSP in eight patients based on history alone (toxic medications, alcohol, inherited neuropathy, peripheral vascular disease, poliomyelitis, and steel-toed shoes) and determined another four cases based on history and/or laboratory abnormalities (renal disease, hypoglycemia, and the metabolic syndrome). Two patients were no longer considered to have DSP after diagnostic testing.

Management changes were either introduced or suggested in 289 patients (63.1%), most commonly altering medications (262 patients). A total of 224 patients (48.9%) had a change in their neuropathic pain medications, with most of these changes involving a GABAergic agent such as gabapentin or pregabalin (145 patients), a tricyclic antidepressant (53 patients), or a serotonin-norepinephrine reuptake inhibitor (49 patients). Potential disease-modifying management change was made in 113 patients (24.7%), including improved diabetes management (45 patients), vitamin treatment (39 patients, 33 with vitamin B12), encouraging diet and exercise (33 patients), changing thyroid medication (10 patients), recommending alcohol cessation (eight patients), and discontinuation of medications thought to be neurotoxic (four patients). Two patients were treated with corticosteroid medication, one with a known mixed connective tissue disease and another with newly diagnosed Sjogren syndrome.

Electrodiagnostic studies, ordered in 353 patients, led to a change in identified cause and/or management in only two patients; in both cases, the change in cause was from a neuropathy diagnosis to a non-neuropathy diagnosis. Neuroaxis MRI, ordered in 65 patients, did not lead to a change in management in any case. The diagnostic testing that most frequently led to management changes included testing for diabetes, thyroid studies, and measurement of vitamin B12 levels.

With a detailed clinical history and several simple and inexpensive laboratory screening studies, community-based neurologists could identify the cause of DSP in nearly 75% of patients presenting for outpatient evaluation. Diagnostic evaluation led to clear diagnosis in 10% of patients with a previously undetermined cause of DSP. The most common new diagnoses were diabetes, prediabetes, thyroid disease, and vitamin B12 deficiency. The use of more expensive electrodiagnostic testing and MRI rarely added to the diagnosis or management of this patient population. Neurologists commonly made management changes, including pain management and treatment of the underlying cause of DSP. Neurologists recommended changes in pain medication for almost half of the patients with DSP, emphasizing the importance of the neurologist in the management of this patient population. The vast majority of these changes involved the three classes of neuropathic pain medication with the best level of evidence to support their use, with rare use of nonsteroidal anti-inflammatory drugs or narcotics.

■ COMMENTARY

In this retrospective cohort study of 458 patients with symptoms of DSP presenting to outpatient community neurologists, neurologists were found to make clinically important contributions to the diagnosis and management of this patient population. Relying on clinical history and several inexpensive diagnostic laboratory studies, the etiology of the DSP could be determined in nearly three-quarters of this patient population. In the majority of patients, neurologists contributed to the management of both the underlying cause of the DSP as well as evidence-based pain management. The use of costly diagnostic studies, such as electrophysiological testing and MRI of the neuroaxis, was not found to increase the diagnostic yield or change patient management. It is recommended that electrophysiological testing be reserved for patients with atypical presentations such as concern for inherited, vasculitic, or demyelinating neuropathy and that MRI of the neuroaxis be reserved for those in whom spinal stenosis is a clinical concern. Compliance with the recommendations of the American Academy of Neurology to screen for diabetes, vitamin B12 deficiency, and para-proteinemia in patients presenting with DSP is reinforced; the data presented in the study suggest that thyroid functions should also be tested routinely. ■

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7. Item 17 must be signed.

Failure to file or publish a statement of ownership may lead to suspension of Periodicals authorization.

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

CME INSTRUCTIONS

To earn credit for this activity, please follow these instructions:
1. Read and study the activity, using the provided references for further research.
2. Scan the QR code to the right or log on to **www.cmecity.com** to take a post-test. First-time users will have to register on the site using the 8-digit subscriber number printed on their mailing label, invoice or renewal notice.
3. Pass the online tests with a score of 100%; you will be allowed to answer the questions as many times as needed to achieve a score of 100%.
4. After successfully completing the test, your browser will be automatically directed to the activity evaluation form, which you will submit online.
5. Once the completed evaluation is received, a credit letter will be e-mailed to you instantly.

CME QUESTIONS

1. **Which of the following statements about sleep is *false*?**
   a. Effective sleep contributes to daytime alertness, good concentration, and good short-term memory.
   b. Obstructive sleep apnea is a risk factor for dementia.
   c. Sedative and hypnotic drugs induce a normal and healthy sleep pattern.
   d. Insomnia impairs cognitive functions.
   e. Humans with good sleep have lower CSF A-beta 42 levels than those who are sleep-deprived.

2. **Chemotherapy-induced peripheral neuropathy:**
   a. does not occur in children.
   b. occurs in about 18% of children treated with chemotherapy.
   c. is preventable.
   d. has been shown in controlled clinical trials to respond to gabapentin.
   e. None of the above

3. **Bedside mental status screening can accurately diagnose mild cognitive impairment.**
   a. True
   b. False

4. **Which of the following statements about Creutzfeldt-Jakob disease (CJD) is *true*?**
   a. CJD can be definitively diagnosed without a brain biopsy.
   b. CJD is a uniformly fatal disease.
   c. CJD can never be transmitted from one person to another.
   d. Brain MRI studies are not helpful in the diagnosis of CJD.

5. **Which of the following statements regarding peripheral neuropathy is *false*?**
   a. Clinical history and examination by a neurologist is sufficient to accurately diagnose and treat most patients with distal symmetrical neuropathy.
   b. MRI of the lumbar spine in patients with a clinical presentation of neuropathy does not add any useful information.
   c. Electrodiagnostic testing (EMGs and nerve conductions) is required to accurately diagnose and treat patients with distal symmetrical neuropathies.
   d. Use of evidence-based diagnostic algorithms for neuropathy patients will save hundreds of millions of dollars in the U.S. health care budget.

CME OBJECTIVES

Upon completion of this educational activity, participants should be able to:

- discuss current scientific data regarding the diagnosis and treatment of neurological disease;
- discuss the pathogenesis and treatment of pain;
- describe the basic science of brain function;
- discuss new information regarding new drugs for commonly diagnosed neurological conditions and new uses for traditional drugs;
- identify nonclinical issues of importance for the neurologist.

[IN FUTURE ISSUES]

Update on Childhood Disorders