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Neurology [ALERT®]

Evidence-based summaries of the latest clinical neurology research

ABSTRACT & COMMENTARY

Mild Traumatic Brain Injury Induces Altered Sleep and Impaired Memory

By Daniel A. Barone, MD, FAASM

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

SYNOPSIS: Traumatic brain injury may induce a chronic state of altered sleep with impaired memory consolidation and mood disorders.

SOURCE: Mantua J, et al. Mild traumatic brain injury chronically impairs sleep- and wake-dependent emotional processing. *Sleep* 2017;40(6).

A single traumatic brain injury (TBI), even when mild (a concussion, for example), can result in lasting consequences. More than 1 million mild TBIs occur each year in the United States, and individuals with a history of chronic (> 1-year prior) mild TBI are at an increased risk of suffering with mood disturbances (i.e., depression, suicide) as well as poor sleep quality and changes in sleep stage proportions.

Mantua et al hypothesized that sleep-dependent memory consolidation would be altered in individuals with chronic mild TBI, the rationale being that disrupted sleep causes or maintains mood disturbances. Additionally, given the known reduction in rapid eye movement (REM) sleep following a mild TBI, a second hypothesis was that sleep's preservation of emotionality might be disrupted in individuals with chronic TBI.

To prove these hypotheses, the authors compared individuals with more than one mild TBI (3.7 ± 2.9 years post injury) against an uninjured population. The TBI group consisted of 40 participants, with an average age of 19.87 years and 75.6% women; the non-TBI group consisted of 41 participants with an average age of 20.15 years and 70.0% women.

Participants viewed negative and neutral images both before and after a 12-hour period containing sleep ("sleep" sub-group) or an equivalent period spent awake ("wake" sub-group). Participants then rated

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images for valence, which is a psychological term for "goodness," and arousal at both sessions. The memory recognition of these images was tested at session two for both groups. Additional testing included nocturnal polysomnogram (PSG), which was recorded in participants' homes using an ambulatory system.

Those in the TBI group had less REM sleep, longer REM latency, and more sleep complaints than the non-TBI group. There were no differences between the TBI and non-TBI sleep groups for total sleep time, sleep efficiency, or time spent awake after sleep onset, nor were there significant differences between the percent of the night spent in other sleep stages.

Sleep-dependent memory consolidation of non-emotional images was present in all participants, but consolidation of negative images was present only in the non-TBI group. The authors noted that sleep-dependent consolidation is optimized when both non-REM and REM sleep are present and sequential, and the negative effects on REM sleep in the TBI group may have hindered consolidation by reducing such REM/non-REM interactions.

Both the TBI sleep and the TBI wake groups found the negative images to be persistently negative at the second presentation. The authors noted that these results are compatible with current theories of depression, which purport that depressive thoughts arise and are perpetuated when an individual is unable to use proper emotional regulation strategies, such as suppression or reappraisal, to habituate when emotional experiences occur.

Multiple TBIs resulted in poorer sleep-dependent memory consolidation and a greater preservation of valence. The authors concluded that individuals who sustain multiple concussions have poorer emotional processing during sleep, during a waking period, and overall, which is consistent with literature on military and athletic activities.

■ COMMENTARY

Disrupted sleep- and wake-dependent emotional processing may contribute to poor emotional outcomes following mild TBI. There are far-reaching implications from this study as roughly one-third of the U.S. population will sustain a mild TBI during their lifetime.

Some issues should be pointed out that were not otherwise mentioned. The PSG testing, while conducted in the participants' homes, could have altered sleep of their own accord (the so-called "first night effect"); it has been shown that objective and subjective sleep measurements seen in depressed insomniacs may be influenced by the monitoring setting. Additionally, the authors mentioned that some participants in both groups used over-the-counter sleep aides. While antihistamines were mentioned, exogenous melatonin was not. This is significant in that melatonin has been shown to increase REM sleep.

On a side note, medical literature is rife with studies demonstrating the complex interplay between neurologic, psychiatric, and sleep disorders. For example, it has been shown that the prevention of sleep following a traumatic event can reduce the formation of traumatic memories and, thus, the development of post-traumatic stress disorder. The information garnered from this study sheds more light on this fascinating interplay and should prompt further investigation. Determining definitively whether TBIs are predictive of emotional dysfunction and whether sleep intervention can repair or rescue sleep-dependent alterations would be a priority. ■

ABSTRACT & COMMENTARY

Is Sleep a Clue to a Modifiable Risk Factor for Alzheimer's Disease?

By Alan Z. Segal, MD

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

SYNOPSIS: Evidence is accumulating that disruptions in sleep patterns, particularly slow-wave and REM sleep, alter amyloid-β production and clearance through the cerebrospinal fluid pathways and may play a role in the development of Alzheimer's disease.

SOURCE: Yo-El S Ju, et al. Slow wave sleep disruption increases cerebrospinal fluid amyloid-β levels. *Brain* 2017;140:2104-2111.

Humans spend approximately one-third of their lives asleep, but the precise function of sleep in the maintenance of a healthy brain remains elusive. There have been limited reports in rodents of a so-called "glymphatic" system that drains the brain of toxins, a process that is accentuated during sleep and blunted in the waking state. Still, considerable variability exists in the amount of sleep we require, with some "short sleepers" functioning on as little as five hours of sleep on a regular basis, with others needing nine or 10 hours to feel rested.

There is ample evidence to suggest that sleep deprivation may be damaging to the brain, as multiple epidemiological studies have shown a connection between sleep impairments and dementia. Three large European cohorts have indicated a risk of Alzheimer's disease (AD) as much as two-fold in older individuals who report sleeping problems. Subjects reported a variety of sleep-related complaints, such as "trouble sleeping," shortened sleep duration (< 7 hours), and the habitual use of sleeping pills.

In the absence of pathologically proven AD, indirect evidence also has been gleaned using biomarkers such as cerebrospinal fluid (CSF) amyloid-β levels and PET scans with amyloid markers (Pittsburgh compound B). Both have shown increases in amyloid among subjects reporting shorter sleep durations and increased wake after sleep onset. It also has been shown that the known correlation between ApoE4 genotype and AD was stronger in subjects who showed fragmented sleep (as measured by actigraphy) compared to subjects who demonstrated a more consolidated sleep architecture. In animal models, using in vivo micro-dialysis, it has been shown that increased neuronal activity directly correlates with amyloid-β in the brain's interstitial fluid and that this amyloid directly leads to increased plaque deposition. Sleep studies in these animals have shown that amyloid-β clearance from the brain is enhanced by sleep and impaired by prolonged wakefulness, with persistently high amyloid-β in the interstitial fluid.

Without the continuous EEG data obtained through polysomnography (PSG), one can only speculate as to whether the total quantity of sleep or specific phases of sleep promote brain health. Slow wave sleep (SWS; with delta frequencies on EEG) arguably is the most "restful" state of sleep and, therefore, the most restorative. It is known that drugs that promote SWS, specifically gamma hydroxybutyrate (GHB) used in the treatment of narcolepsy, can increase daytime wakefulness and vigilance. The brain also may "crave" rapid eye movement (REM) sleep, but in contrast to SWS, REM sleep has a more poorly understood neuroanatomy and neurochemistry. Although REM is associated with muscle relaxation and may be physically restorative, the active cortical activity seen in REM more closely matches the waking state.

Yo-El et al subjected 22 participants (aged 35-65 years, with a mean of 54 years) to an experimental protocol in which their SWS was disrupted artificially. During a polysomnogram, as delta EEG activity (as quantified by the "delta power" in spectral analysis) was shown to rise, a series of progressively louder tones was delivered through headphones until the subject's EEG demonstrated an arousal out of SWS. Each subject had two PSGs, one experimental and one sham, in which there was no tonal disruption of SWS. Subjects accrued an average of seven minutes of SWS in the sham condition and none with SWS disruption. REM sleep duration also was shortened in the experimental condition.

CSF in each subject was obtained the following morning. SWS disruption was associated strongly with increases in CSF amyloid-β ($r = 0.610$; $P = 0.009$). There was no relationship between amyloid-β levels and any other measure of sleep (total sleep time, non-REM sleep, REM-sleep, or sleep efficiency). The effect of SWS disruption was specific for amyloid-β and was not shown for other markers, such as YKL-40 (an astrocyte-derived inflammatory protein) or tau.

■ COMMENTARY

These data can be considered a landmark discovery in our understanding of the basic functions of sleep and might have major societal implications. Could sufficient, high-quality sleep blunt cognitive impairments later in life and actually protect against AD? At a minimum, these data provide convincing evidence that SWS has a direct beneficial effect on the amyloid neurochemistry of the brain and adds support to prior data suggesting that sleep allows the brain to "wash out" toxins.

Despite the dramatic nature of these results, however, it is puzzling that such major effects on CSF amyloid-β occurred with only a very small (seven minutes on average) SWS deprivation. Middle-aged subjects studied here, not unexpectedly, got a minimal amount of SWS. While delta sleep may occupy as much as 15-20% of the night in a child or adolescent, SWS only occurs during 3-5% of the night in middle age. Furthermore, in the elderly, no SWS occurs at all. Therefore, it remains possible that sleep disruption later in adulthood and into senescence is not the cause of cognitive decline, but merely an epiphenomenon of the degenerating brain. Failure to achieve SWS is not a pathological state, but merely an effect of normal aging. ■

ABSTRACT & COMMENTARY

P-syn in Nerve Fibers on Skin Biopsy May Help Diagnose Dementia with Lewy Bodies

By Harini Sarva, MD

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

SYNOPSIS: This study compared 18 subjects diagnosed with dementia with Lewy bodies (DLB), 23 with nonsynucleinopathy dementia, and 25 healthy controls and demonstrated that phosphorylated alpha-synuclein was found only in the skin nerve fibers of DLB subjects, helping distinguish this type of dementia from other types.

SOURCE: Donadio V, et al. A new potential biomarker for dementia with Lewy bodies. *Neurology* 2017;89:318-326.

The authors enrolled 18 subjects who met the criteria consistent with dementia with Lewy bodies (DLB): rapid cognitive decline and parkinsonism developing within one year, rapid eye movement (REM) sleep behavior disorder, fluctuating cognition, visual hallucinations, and neurogenic orthostatic hypotension. Seventeen of the 18 tested positive on DaTscan, suggestive of presynaptic dopaminergic dysfunction, and abnormal cardiac uptake of iodine-123-meta-iodobenzylguanidine, suggestive of cardiac postganglionic sympathetic denervation, both of which supported the diagnosis of DLB clinically. One patient refused both tests, but the clinical picture was consistent with DLB, and the patient was included in the study. This cohort was compared with 23 subjects with dementia of different pathologies (NSD): 13 with Alzheimer's disease confirmed with appropriate cerebrospinal fluid beta amyloid-42, total tau, and phosphorylated tau; six with frontotemporal dementia associated with C9orf72 repeat expansion (4), progranulin mutation (1), and TDP43 mutation (1); and four with vascular dementia. Peripheral neuropathy was evaluated in these subjects with testing for diabetes; B12 deficiency; and microbiological, autoimmune, paraneoplastic, and thyroid disorders as well as electrophysiological analysis. Twenty-five healthy, age-matched controls also were evaluated.

Those with DLB and NSD had similar disease duration, Mini-Mental State Examination (MMSE) scores, and brief mental deterioration battery (BMDM) scores. Twelve of the DLB subjects had dementia at the onset, whereas six had parkinsonism. Phosphorylated alpha-synuclein (P-syn) was not found in any skin sample in either the NSD group or the healthy controls. Those with DLB showed more P-syn in a proximal to distal distribution, with more found in the cervical region than in the thigh or leg. For example, in one of two sets of samples taken, the abnormal deposits were found in 95%, 89%, and 76% of DLB patients in the cervical region, thigh, and leg, respectively. P-syn also was found more frequently in adrenergic neurons rather than in cholinergic vasoactive intestinal polypeptide-positive fibers, such as those found in the sweat glands. Those with autonomic dysfunction had a higher frequency of P-syn compared to those without autonomic dysfunction (97% vs. 71% of samples analyzed). In addition, those with autonomic dysfunction had homogenous P-syn distribution, whereas those without had the more proximal to distal gradient. The amount of skin samples with P-syn also correlated with Unified Parkinson's Disease Rating Scale (UPDRS) scores and with leg arrector pilum innervation rate, but not with MMSE score, disease duration, or age of onset. Epidermal and autonomic skin innervation were poor, particularly in the leg in DLB subjects when compared with NSD and healthy controls. When comparing DLB subjects with and without autonomic dysfunction, lower leg autonomic innervation scores were significantly different both for the sweat glands and arrector pilum muscle, but no differences were noted in the cervical region or thigh.

■ COMMENTARY

This study highlights three important features of DLB, further adding to our knowledge of the clinical phenotype. First, P-syn staining may assist in accurately diagnosing DLB earlier in the disease course. Second, autonomic neuropathy may be an additional feature of DLB, and third, those with autonomic dysfunction have more widespread P-syn deposition. This observation is important because clinically, DLB can be indistinguishable from Alzheimer's at times. A skin biopsy also is a safe and easy procedure with few adverse events. Easy access to cutaneous P-syn would enable earlier diagnosis of DLB and potential development of DLB-specific therapies. However, the results of this small study need to be replicated in larger, more diverse cohorts. In addition, the staining procedure for P-syn is challenging, and expert pathological analysis is required to correctly detect its presence.

The most important and challenging underlying issue that can limit the utility of this testing is the suboptimal specificity of the diagnostic criteria of DLB. The

presence of autonomic dysfunction in this study can be used to distinguish DLB from NSD but not necessarily from multiple system atrophy (MSA), another synucleinopathy with autonomic dysfunction. MIGB and DaTscan also are positive in MSA; thus, potential therapeutic trials for DLB may incorporate other synucleinopathies. Finally, the authors noted that DLB can have atypical features, such as longer duration of disease and young age of onset (before age of 65), limiting the generalizability of these data. ■

ABSTRACT & COMMENTARY

Risk Factors for Seizures in Critically Ill Patients Monitored by Continuous EEG

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

SYNOPSIS: Investigators prospectively analyzed 72-hour continuous electroencephalograms to identify clinical and electroencephalogram risk factors for having seizures and developed a model for "time-dependent" seizure risk. Electrographic seizures occurred in 23% of all patients. The only significant clinical predictors of seizures were presence of coma and prior clinical seizure history.

SOURCE: Struck AF, et al. Time-dependent risk of seizures in critically ill patients on continuous electroencephalogram. *Ann Neurol* 2017; July 6. [Epub ahead of print].

Non-convulsive seizures (NCS) are reported in about 20% of critically ill patients,[1] typically with little to no overt clinical signs, thus requiring identification with continuous electroencephalogram (CEEG).[2] With recent studies suggesting that NCS can have significant adverse effects on the brain, some current practice guidelines recommend ordering CEEG in critically ill patients who are at increased risk for seizures and with unexplained altered or fluctuating mental status.[2] However, the question always remains about how long monitoring should be continued, particularly in locations where resources are limited. A commonly cited study from 2004 showed that nearly 90% of NCS in critically ill patients were recorded within the first 24 hours,[1] but this study did not discern specifically which patients were at greatest risk.

Struck et al developed a model for "time-dependent" electrographic seizure risk in critically ill patients based on clinical risk factors and CEEG abnormalities. At two academic hospitals, 665 eligible critically ill patients were monitored prospectively on CEEG for 72 hours. One of the three authors read and scored the CEEGs after undergoing a certification test. Both the presence and time to emergence of seizures, as well as rhythmic or periodic patterns, were recorded. Clinical characteristics, such as gender, presence of brain injury, history of epilepsy or recent acute seizures, coma, and presence of focal neurological findings, were recorded prospectively.

Electrographic seizures occurred in 151 of 665 (23%) patients. The only clinical risk factors that were significant independent predictors for seizures were 1) prior clinical seizures (history of epilepsy and/or presence of acute clinical seizures), and 2) coma. In terms of EEG findings, lateralized periodic discharges (LPDs), lateralized rhythmic delta activity (LRDA), and brief potentially ictal rhythmic discharges (BIRDs) were significantly associated with electrographic seizures, whereas sporadic epileptiform discharges, bilateral independent periodic discharges, and lateralized rhythmic spike-and-wave were not statistically significant. The median observed time of EEG "risk pattern" emergence (i.e., any epileptiform abnormality) was four minutes and of seizure emergence was 44 minutes. However, using a "multistate survival analysis," the authors attempted to identify the "decaying" risk of seizures as a function of EEG duration, abnormal EEG findings, and clinical risk factors. They noted that seizure risk declined quickly if EEG abnormalities were not seen and there were no clinical risk factors. As an example, if a patient had no seizure history and was not comatose, a negative routine EEG of at least 30 minutes would be sufficient to place seizure risk at < 5% over the next 72 hours. However, if there was an EEG abnormality or if there was one or more clinical risk factor, patients would need at least 15-44 hours of CEEG.

■ COMMENTARY

Critically ill patients can have multiple reasons for altered or fluctuating mental status, but given that nearly 20% can have NCS, CEEGs are ordered with increasing frequency in ICUs. However, some facilities have limited resources, so having guidelines would be meaningful. In this study, 23% of patients had electrographic seizures, comparable to previous studies. What is most noteworthy about this study, however, is looking at seizure risk in a "time-dependent" manner. If a patient had no history of previous clinical seizures and was not comatose, this study suggested that routine EEG may be sufficient to rule out seizures for unexplained altered or fluctuating mental status, assuming no epileptiform abnormalities

are seen. However, if any of these EEG abnormalities are appreciated, particularly LPDs, LRDA, or BIRDs, within the first 30 minutes of recording or if a patient has one of these two clinical risk factors, then EEG should be extended to at least 24 hours. If a patient has both EEG "risk patterns" and one of these clinical risk factors, then the authors recommended extending the recording to at least 48 hours. ■

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2. Struck AF, et al. Time-dependent risk of seizures in critically ill patients on continuous electroencephalogram. *Ann Neurol* 2017; July 6. [Epub ahead of print].

ABSTRACT & COMMENTARY

EEG-based Metrics After Severe Brain Injury

By Peter B. Forgacs, MD

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

SYNOPSIS: In this cohort study of 104 patients with disorders of consciousness, the authors demonstrated a strong correlation between EEG-based metrics and clinical diagnosis using quantitative behavioral scales, brain metabolism as measured by PET, and clinical outcomes at one year.

SOURCE: Srivas C, et al. Brain networks predict metabolism, diagnosis and prognosis at the bedside in disorders of consciousness. *Brain* 2017;140:2120-2132.

In the last 15-20 years, there have been substantial efforts to accurately assess the potential preservation of organized higher-level neuronal functions in patients with limited or absent bedside evidence of consciousness. Such behavioral states typically arise after a severe brain injury and patients may have prolonged disorders of consciousness (DOC). Categories within DOC include coma (state of unarousable unresponsiveness), vegetative state (VS; distinguished from coma by intermittent eye opening despite unresponsiveness), and minimally conscious state (MCS; characterized by intermittent or inconsistent responses to external stimuli). The current gold standard to diagnose DOC is a standardized bedside clinical scale, the Coma Recovery Scale–Revised (CRS-R). However, obtaining CRS-R requires experienced professionals, and the rate of misdiagnosis in DOC using clinical assessments is high. This study seeks to validate objective measurements that can complement clinical evaluations in patients with DOC.

Recent studies focused on advanced functional neuroimaging (such as functional MRI or ^{18}FDG-PET) to assess residual neuronal functions have provided useful information about structural and functional integrity of brain activity in DOC patients. However, such imaging studies are hindered by logistical constraints that limit their application to studies in research laboratories. Therefore, in recent years, considerable efforts have been devoted to applications of electroencephalogram (EEG) to assess functional brain integrity in patients with DOC. EEG is widely available in most clinical environments, it is easily affordable, and it can be repeated many times without significant risks. In addition, EEG is a direct measure of neuronal electrical activity and allows assessments of functional brain integrity without active participation of patients.

A total of 104 patients were involved in this study — 89 had DOC (23 in VS, 66 in MCS), 11 emerged from MCS, and four patients were in a locked-in state. In addition, 26 control subjects were included in the analysis. A 256-channel high-density EEG was used in all subjects assessed. Resting EEG analyses included relative spectral power estimates in three conventional frequency bands (delta [0-4 Hz], theta [4-8 Hz], and alpha [8-13 Hz]) and an assessment of synchronicity between corresponding EEG electrode pairs. These latter measures also were used to create connectivity matrices that were further applied to calculate seven different graph-theoretical measures of local and global network connectivity (a total of 21 metrics for the three frequency bands analyzed). Each metric was used to estimate the ability to discriminate between evidence of consciousness compared to standardized bedside exam (CRS-R), PET-based criteria for metabolic patterns as related to behavioral diagnosis, and clinical outcome at one-year after study assessments. In addition, these measures were used to train a classifier to predict evidence of consciousness in an individual patient in relation to each of the above-mentioned measures. To further validate their accuracy, the classifiers also were tested in out-of-sample subjects who were not used for training of the classifier.

The authors successfully demonstrated that their EEG metrics of network integrity were associated both with bedside behavioral diagnoses and metabolic

activity patterns of the DOC patients, as well as long-term outcomes. Specifically, they showed that the most robust predictors of behavioral level were connectivity measures in the alpha band, especially between lateral and medial frontoparietal areas, consistent with previous electrographic and neuroimaging studies with highly comparable accuracy. Furthermore, they also found a significant correlation between delta-frequency measures and clinical outcomes at one year; stronger delta band connectivity in the central and parietal networks predicted worse outcomes.

■ COMMENTARY

This study represents an important step toward development of EEG metrics that can reliably predict level of consciousness in patients with DOC and are suitable to complement bedside clinical assessments. These results provide further evidence that EEG-based assessments of ongoing network-level cerebral activity could be used in everyday clinical practice in the future. The accuracy of the measures applied here is comparable with other, more complex EEG-based (e.g., TMS-EEG) or neuroimaging-based methodologies, but offer a much simpler, near-automated method for EEG analysis. Eventually, these methods will be deployed easily at the patients' bedside and may provide valuable information about level of consciousness and complement clinical examinations.

However, the methods applied here used high-density (256-channel) EEG recordings that typically are not available in general clinical practice. As suggested, further work is needed to validate these approaches using a reduced number of electrodes, possibly using customized placement over the connectivity hubs demonstrated in this study. In addition, while the methods applied here are almost completely automated, they still require EEG pre-processing by experts using visual inspection of raw EEG recordings to remove artifacts, such as noisy data from movements, muscle activity, or environmental noise. Furthermore, they require complex analyses currently only available in research settings. ■

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ABSTRACT & COMMENTARY

Optimizing Electromyography in ALS

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: In the appropriate clinical setting, electromyography studies of multiple, distal muscle groups in three separate spinal regions showing acute and chronic denervation, are pathognomonic for the diagnosis of amyotrophic lateral sclerosis.

SOURCE: Babu S, et al. Optimizing muscle selection for electromyography in amyotrophic lateral sclerosis. *Muscle Nerve* 2017:56:36-44.

Although electrodiagnostic findings of active denervation on needle electromyography (EMG), comprising positive sharp waves and fibrillation potentials, are not pathognomonic for amyotrophic lateral sclerosis (ALS) and may be seen in any denervating process, these abnormalities are the sine qua non for making a diagnosis of ALS in the appropriate clinical setting. Revised El Escorial ALS diagnostic criteria require evidence of active and chronic denervation, the latter defined as large, unstable, polyphasic motor unit potentials of increased duration with a reduced interference pattern in cervical, thoracic, and lumbar regions or in bulbar muscles plus two spinal regions. In each of the cervical and lumbosacral regions, at least two muscles innervated by different roots and different peripheral nerves must have positive sharp waves or fibrillation potentials. Given the innate discomfort of EMG, which muscles and combination of muscles might offer the highest yield, allowing testing to be minimized as much as possible?

To answer the above question, Babu et al performed a retrospective chart review of 617 consecutive patients, seen at the Cleveland Clinic between Jan. 1, 2003, and Dec. 31, 2012, with a clinical diagnosis of ALS and who underwent EMG testing. Patients with underlying sensorimotor polyneuropathy, or cervical or lumbosacral spondylomyelopathy were excluded. To avoid possible neuropathic confounding influences, patients aged 60-75 years with absent sural sensory responses on nerve conduction studies also were excluded, even in the absence of clinical polyneuropathy. Patients with mononeuropathies were included, but muscles innervated by the affected nerves were excluded from analysis. Reanalysis of EMG findings using Awaji criteria, allowing fasciculation potentials to serve as evidence of active denervation when chronic denervation is concomitantly present, also was undertaken. Statistical analysis encompassed the Fisher exact test and pair-wise comparison of proportions.

Among 617 screened patients, 354 met eligibility criteria, including 64 with definite ALS, 204 with probable ALS, and 86 with clinically probable, laboratory-supported ALS, as defined by consensus guidelines.[1] Mean age was 60.5 years, 89% were Caucasian, 5% were African American, and the male to female ratio was 1:2. EMG findings from 5,315 muscles examined in these patients revealed that regardless of where the first signs of disease occurred, distal limb muscles were the most sensitive in providing evidence of lower motor neuron dysfunction, in the form of active and chronic denervation. In the arm, these muscles included the first dorsal interosseous, the abductor pollicis brevis, and the abductor digiti minimi, and, in the leg, the tibialis anterior, the medial gastrocnemius, and the tibialis posterior/flexor digitorum longus. Abnormalities also were more likely to be found in muscles of the initially affected limb compared to limbs subsequently affected. Studying six upper and five lower extremity muscles offered a > 98% positive yield, and beginning with a proximal muscle in the arm and leg, such as the deltoid and the quadriceps, respectively, and then examining a distal muscle, is recommended.

■ COMMENTARY

Cervical spondylotic amyotrophy (CSA), presenting with regional muscle atrophy, muscle weakness, and minimal long tract signs, often requires clinical differentiation from ALS. Repetitive nerve stimulation (RNS) studies may help differentiate between them. Among 53 ALS and 37 CSA patients, RNS of the abductor pollicis brevis, upper trapezius, and deltoid muscles revealed an abnormal decremental response in 31%, 51%, and 75% of the ALS patients, but only in 3%, 0%, and 20% of the CSA patients, respectively. Abnormal RNS of the trapezius is 100% specific for ALS as opposed to CSA, whereas absence of decrement in the deltoid, in patients with upper limb onset, may exclude ALS. ■

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CME QUESTIONS

1. **Traumatic brain injury may alter sleep in which of the following ways?**
   a. Less total sleep time
   b. Fewer sleep complaints
   c. Excessive daytime sleepiness
   d. Less REM sleep
   e. Longer time to sleep onset
2. **Which of the following sleep impairments produces increases in CSF amyloid levels?**
   a. Decreased total sleep time
   b. Decreased duration of non-REM sleep
   c. Decreased duration of REM sleep
   d. Decreased duration of slow wave sleep
   e. Poor sleep efficiency
3. **In amyotrophic lateral sclerosis, which of the following muscles is among the most sensitive to examine using needle electromyography?**
   a. First dorsal interosseous
   b. Abductor pollicis brevis
   c. Abductor digiti minimi
   d. All of the above
   e. None of the above
4. **Which pair of clinical characteristics had the highest significant association with an increased risk of electrographic seizures in critically patients monitored for 72 hours on continuous EEG?**
   a. Presence of brain injury and coma
   b. Focal neurological findings and history of prior clinical seizures
   c. Coma and history of prior clinical seizures
   d. Presence of brain injury and focal neurological findings
5. **What is the current gold-standard to diagnose disorders of consciousness, i.e. vegetative state, minimally conscious state, or emergence from minimally conscious state?**
   a. Electroencephalogram
   b. Positron emission tomography
   c. Coma Recovery Scale–Revised
   d. Functional MRI

[IN FUTURE ISSUES]

Advances in Brain Tumor Treatment