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ABSTRACT & COMMENTARY

Effect of Sleep on Levodopa-Induced Dyskinesia in Parkinson's Disease

By Daniel A. Barone, MD, FAASM

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

SYNOPSIS: Parkinson's disease is associated with sleep disorders commonly. Disrupted sleep patterns appear to make dyskinesias worse in patients treated with levodopa therapy.

SOURCE: Amato N, Manconi M, Moller JC, et al. Levodopa-induced dyskinesia in Parkinson's disease: Sleep matters. *Ann Neurol* 2018; Oct 17. doi: 10.1002/ana.25360. [Epub ahead of print].

It is well known that Parkinson's disease (PD) comprises a spectrum of motor and nonmotor symptoms that tend to change as the disease progresses. Levodopa, a medication ubiquitously used in PD patients, can have paradoxical effects on PD. Levodopa controls motor symptoms for several years, but it later induces motor fluctuation and abnormal involuntary movements, heretofore known as levodopa-induced dyskinesias (LIDs).

The synaptic homeostasis hypothesis (SHY) is a proposed mechanism to explain why the brain needs sleep for retention of memories. In wakefulness, learning requires a strengthening of certain synaptic connections, unsurprisingly increasing the need for neuronal cellular energy. In sleep, there is a restoration of cellular homeostasis through down-regulation of other synapses. Additionally, slow-wave activity (SWA) during non-rapid eye movement (NREM) sleep particularly contributes to adjustment of plasticity and cortical excitability.

In prior studies, sleep-deprived rodents that were exposed to levodopa developed earlier and more severe LID than those that were not sleep deprived. Amato et al explored the correlation, in humans,

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between objective sleep parameters and clinical features of different subpopulations of PD patients.

The authors recruited 36 subjects with PD and divided them into three groups: 1) de novo (DNV; n = 9): patients recently diagnosed and naïve to dopaminergic therapy other than rasagiline; 2) advanced (ADV, n = 13): patients not demonstrating LID with their habitual therapy but having the end-of-dose or wearing-off phenomenon; and 3) dyskinetic (DYS, n = 14): advanced patients experiencing motor fluctuations and showing LID.

These subjects, as well as 12 age-matched controls, underwent whole-night video polysomnography high-density EEG (vPSG-hdEEG), preceded by one week of actigraphy. Then, the SWA content of the vPSG-hdEEG was divided into 10 equal parts, noted from T1 to T10. Parts T2, T3, and T4 correlated with early sleep, and parts T7, T8, and T9 represented late sleep.

As expected, the authors found that early sleep control subjects showed a significantly greater amount of SWA compared to all PD patient groups ($P < 0.01$). On further analysis, SWA also occurred more often in the DNV group compared to the other patient groups ($P < 0.01$). SWA also was greater in the ADV group compared to the DYS group ($P < 0.01$); the DYS group had the lowest SWA overall. Additionally, the authors found a significant difference in SWA between early and late sleep in the control (n = 7), DNV (n = 5), and ADV groups (n = 9; $P < 0.01$) but not in the DYS group (n = 10). Furthermore, while the correlation between SWA and disease duration was positive in both the DNV and ADV groups, it was negative in the DYS group.

The authors believed the correlation between SWA and disease duration in both the DNV and ADV groups might reflect compensatory mechanisms within the SHY framework that could be ineffective in the DYS group. Similarly, they attempted to explain the lack of difference between the early sleep and late sleep SWA in the DYS group as a potential failure of the homeostatic mechanism proposed in the SHY.

Amato et al concluded that there is a clear association between sleep and LID. Considering the homeostatic hypothesis, and that researchers cannot determine a causative role for the lack of SWA reduction in the emergence of LID, they can suggest an association between sleep and some clinical phenotypes of PD, as well as a relationship between sleep disruption and LID.

[A better understanding of sleep, REM behavior disorder, and Parkinson's disease may prove vital to one day preventing or curing Parkinson's disease.]

■ COMMENTARY

This study was small but well done. As the authors noted, PSG studies in the PD population have shown conflicting results regarding changes in sleep efficiency, total sleep time, and sleep stages in PD patients compared to controls. What is unique about the Amato et al study is that sleep architecture was examined with respect to the disease stage and to the presence or absence of motor fluctuations and LID, allowing for a more accurate detection of differences that otherwise would not be defined clearly in a heterogeneous group. Future studies examining the link between sleep and PD should adopt a similar framework.

The link between PD and sleep disorders is becoming more prevalent in the medical literature, and an improved understanding of both facets of this equation will be of great help to researchers and clinicians. Of particular interest is the intriguing relationship between REM behavior disorder as an early marker of PD and PD-related conditions (i.e., multiple system atrophy, dementia with Lewy bodies). A better understanding of sleep, REM behavior disorder, and PD may prove vital to one day preventing or curing PD. ■

ABSTRACT & COMMENTARY

Utility of Ictal Magnetoencephalography for Identifying Seizure Onset Zone

By Kimberly Pargeon, MD

Assistant Professor of Clinical Neurology, Weill Cornell Medical College

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

SYNOPSIS: In a review of 377 magnetoencephalography (MEG) studies in epilepsy patients undergoing presurgical workup, 44 patients were found to have one or more seizures during routine recordings, lasting up to a mean of 51.2 minutes. Ictal MEG provided unique localizing data in about one-third of patients. For patients with frequent seizures or reliably induced seizures, MEG may be a useful supplemental tool for medically refractory epilepsy patients undergoing presurgical evaluation.

SOURCE: Alkawadri R, Burgess RC, Kakisaka Y, et al. Assessment of the utility of ictal magnetoencephalography in the localization of the epileptic seizure onset zone. *JAMA Neurol* 2018;75:1264-1272.

Magnetoencephalography (MEG) is being used more widely for evaluating patients considering epilepsy surgery, although its availability is limited. It can add additional information for guiding phase II implantation, particularly in patients who are nonlesional on imaging or in whom scalp electroencephalogram (EEG) is nonlocalizing. MEG is noninvasive with good temporal and spatial resolution.[1,2] It has several other advantages over scalp EEG, including the fact that it requires less cortical spread for detection of spike activity (3-4 cm^2 vs. 6-20 cm^2 for EEG), lacks distortion by intervening tissues (skull, skin, cerebrospinal fluid), and provides better spatial resolution (2-3 mm vs. 7-10 mm for EEG).[2] Since MEG records tangential dipoles, it is especially useful for identifying epileptic foci associated with focal cortical dysplasias, which often are located at the bottom of deep sulci and are tangential to the surface.[2] Lastly, MEG also can be used for functional mapping of eloquent cortex,[2] either in lieu of or as an adjunct to functional magnetic resonance imaging (MRI) or Wada testing.

Alkawadri et al retrospectively reviewed 377 consecutive MEG studies at a single tertiary care center (Cleveland Clinic) in patients with medically refractory epilepsy undergoing presurgical evaluation from March 2008 to February 2012 to identify patients experiencing epileptic seizures during their studies. Typically, MEG was done in patients with discordant data or with non-localizing EEGs. Recordings lasted an average 51.2 minutes, using a whole-head, 306-channel MEG system, along with 21 channels of scalp EEG. Dipoles were coregistered with the patient's brain MRI (magnetic source imaging, MSI). Ictal onset was defined as the initial period of "evolving rhythmic oscillations temporally related to the clinical and EEG onset of the patient's typical seizures."[1] Data were reviewed by two epileptologists with expertise in MEG interpretation.

Forty-four patients had at least one seizure during their routine MEG: 25 patients (57%) had one seizure; six patients (14%) had two seizures; seven patients (16%) had three to 20 seizures; five patients (11%) had more than 20 seizures; and one patient (2%) presented for partial status epilepticus localization. The mean age of patients with seizures was 19.3 years, and they had a baseline seizure frequency of 182 seizures per month (compared to 98.7 seizures per month for excluded patients).[1]

Compared to scalp EEG, MEG tended to show more focal onsets in 26 patients (59%), as compared to 17 patients (39%) on scalp EEG. In fact, MEG provided unique localizing findings not appreciated on simultaneous scalp EEG in 16 patients (36%), including three patients (7%) with simple partial seizures with MEG changes without scalp EEG correlates, six patients (14%) with either nonlocalizable or generalized EEG changes, and four patients (9%) with discordant localization compared to EEG. In the latter four patients, intracranial recordings later confirmed the MEG localization. Dipole fitting was possible in 80% of patients (n = 35) with interictal discharges and 66% (n = 29) with ictal discharges. There were eight patients in whom ictal MEG provided unique findings without interictal EEG findings, seven of whom had no MRI findings, and five of whom had nonlocalizing findings on video EEG.

When presurgical data were reviewed in surgical management conference, epilepsy was localized or lateralized in 31 patients (70%) based on expert consensus and was nonlocalizable in the remaining 13 patients (30%). However, ictal MEG provided further localizing data in five of these 13 patients (38%). Eleven patients (25%) underwent phase II monitoring. For eight of these patients, seizure onset could be localized with intracranial EEG, and MEG dipole analysis was possible, with ictal MEG dipoles

correlating to the lobe of onset in seven of eight patients (88%).

■ COMMENTARY

The pivotal finding is that ictal MEG provided unique localizing data for about one-third of patients who otherwise were difficult to localize with scalp EEG and other modalities. Per the authors, ictal events can be recorded in a "substantial" number of patients undergoing routine MEG, with 12% of their patients experiencing at least one event during a one-hour recording. However, the average number of seizures per month in patients with an "ictal" MEG was 182, equating to about six seizures per day. Thus, the chance of capturing an ictal event likely would be low for patients who do not experience daily seizures, unless events can be induced reliably. Also, although MEG is not sensitive to intervening tissues, movement artifact during seizures, particularly head movements, must be suppressed. Alkawadri et al recommended not only considering the incorporation of ictal MEG into patients' presurgical analysis, but also timing ictal MEG recordings to be done when patients are admitted to the epilepsy monitoring units when antiepileptic drugs already are reduced. However, at most centers, access to MEG is extremely limited, with very few hospitals having a MEG on site. Overall, in the hands of a capable interpreter and in a patient with frequent seizures, ictal MEG may be another tool for better localizing the seizure onset zone. ■

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ABSTRACT & COMMENTARY

Apolipoprotein E and CSF Levels in Men and Women With Alzheimer's Disease

By Lisa Mosconi, PhD

Associate Professor of Neuroscience in Neurology; Associate Director, Alzheimer's Prevention Clinic/Department of Neurology, Weill Cornell Medical College

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

SYNOPSIS: Apolipoprotein E epsilon 4 (APOE4) genotype, the stronger genetic risk factor for late-onset Alzheimer's disease, negatively affects cerebrospinal levels of tau protein in a sex-dependent manner, whereby the effect of APOE4 is stronger in women than men.

SOURCE: Hohman TJ, Dumitrescu L, Barnes LL, et al. Sex-specific association of apolipoprotein E with cerebrospinal fluid levels of tau. *JAMA Neurol* 2018;75:989-998.

It long has been known that the prevalence of Alzheimer's disease (AD) is higher in women than in men, even accounting for women's increased longevity relative to men.[1] Further, the epsilon 4 variant of the apolipoprotein E gene (APOE4), the strongest genetic risk factor for late-onset AD, increases AD risk in a sex-dependent manner. The strength of the association varies by age, with female APOE4 carriers aged 55 to 70 years having the highest risk.[2] To address the gender disparity in AD prevalence, efforts toward understanding sex-specific differences in disease etiology, manifestation, and progression have begun to emerge.

Hohman et al carried out a multi-cohort study that combined data from 10 longitudinal cohort studies of normal aging and AD. The goal of the study was to examine sex-dependent effects of APOE genotype on markers of AD pathology in vivo and ex vivo. The first set of analyses focused on four in vivo date sets that included cerebrospinal fluid (CSF) levels of beta-amyloid 42, total tau, and hyperphosphorylated tau measures collected from 1,798 patients, 48% of whom were women. The second set of analyses focused on six autopsy data sets leveraging direct measures of AD neuropathology, including Consortium to Establish a Registry for Alzheimer's Disease (CEDAR) staging for neuritic plaques and Braak staging for neurofibrillary tangles, obtained from 5,109 patients, including 55% women.

Of the 1,798 patients in the CSF biomarker cohort, 862 were women, 226 had AD, 1,690 were white, and the mean age was 70 years. Of the 5,109 patients in the autopsy cohort, 2,813 were women, 4,953 were white, and the mean age was 84 years.

After correcting for multiple comparisons, the authors found a statistically significant interaction between APOE4 and sex on CSF total tau and phosphorylated

Table 1: APOE-ε4 Association With CSF Tau in Men and Women

	Standardized beta (95% confidence interval)				
	BIOCARD	**WRAP**	**ADNI**	**VMAP**	**Summary**
Men	-0.04 (-0.22 to 0.14)	-0.20 (-0.47 to 0.07)	0.26 (0.19 to 0.34)	0.28 (1.10 to 0.46)	0.20 (0.14 to 0.27)
Women	0.10 (-0.04 to 0.25)	0.24 (0.05 to 0.43)	0.47 (0.39 to 0.54)	0.38 (0.09 to 0.66)	0.37 (0.31 to 0.43)

BIOCARD: Biomarkers of Cognitive Decline Among Normal Individuals; WRAP: Wisconsin Registry of Alzheimer's Prevention; ADNI: Alzheimers Disease Neuroimaging Initiative; VMAP: Vanderbilt Memory and Aging Project
Source: Hohman TJ, Dumitrescu L, Barnes LL, et al. Sex-specific association of apolipoprotein E with cerebrospinal fluid levels of tau. *JAMA Neurol* 2018;75:989-998.

tau ($P \leq 0.001$). APOE4 showed a stronger association among women than men. On post-hoc analysis, this sex difference was present in amyloid-positive individuals but not amyloid-negative individuals. (*See Table 1.*) No interactions between APOE4 and sex were found on postmortem measures.

■ COMMENTARY

These findings provide robust evidence of sex differences in the association between APOE4 and CSF tau levels. The authors found the effect of APOE was stronger in women than men. The observed sex difference was driven by amyloid-positive individuals, which suggests that APOE may confer sex-specific risk for downstream neurodegeneration in the presence of enhanced amyloidosis. These results point to several sex-driven mechanisms that could underline this sex difference in tau, especially hormonal changes that occur during and after menopause being the strongest candidate pathway. For example, other researchers have found evidence that decreased estrogen levels in women could lead to a more severe downstream response to amyloidosis,[3] an effect that could be enhanced among APOE4 carriers. Alternatively, late-life changes in estrogen levels in women directly affect tau. In fact, in female rats, estradiol appears to protect against tau hyperphosphorylation.[4]

These data are consistent with recent brain imaging studies showing that, among middle-aged women at risk for AD, those at the perimenopausal and postmenopausal stages exhibit emergence and progression of an AD endophenotype characterized by increasing beta-amyloid deposition, declines in glucose metabolism, and reduced brain volumes.[5-7] Amyloid deposition was more pronounced in APOE4 carriers than noncarriers.[5] No such abnormalities were observed in age-matched men, suggesting that AD-related pathological changes and their downstream effects on neuronal function affect women's brains earlier than men's brains.More research is needed to evaluate the genetic drivers of plaques, tangles, neurodegeneration, and cognitive impairment in a sex-specific manner to identify novel pathways of risk. ■

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ABSTRACT & COMMENTARY

Correlation of Electromyography With Pathology in Myopathy

By Michael Rubin, MD

Professor of Clinical Neurology, Weill Cornell Medical College

Dr. Rubin reports he is a consultant for Merck Sharp & Dohme Corp.

SYNOPSIS: A detailed analysis of electromyography features showed a high correlation with muscle pathology. However, pathologic changes on muscle biopsy may be present even with a totally normal electromyogram.

SOURCE: Sener U, Martinez-Thompson J, Laughlin RS, et al. Needle electromyography and histopathologic correlation in myopathies. *Muscle Nerve* 2018; Nov. 10. doi: 10.1002/mus.26381. [Epub ahead of print].

Aside from serum creatine kinase and aldolase, the laboratory investigation of suspected myopathy often includes needle electromyography (EMG) and muscle biopsy. Is there a correlation between specific findings on EMG and pathological changes on muscle biopsy that might allow the electromyographer to predict specific pathologic changes on biopsy, based on EMG abnormalities?

In this retrospective study, Sener et al reviewed records of 224 consecutive patients seen for muscle biopsy at Mayo Clinic sites in Jacksonville, Florida, and Rochester, Minnesota. Inclusion criteria required that the EMG be performed prior to the muscle biopsy, and that the muscle biopsied was studied by EMG but was contralateral to the one examined. On review of EMG studies, the authors specifically noted the presence of fibrillation potentials, myotonic discharges, and short duration motor unit potentials. For muscle biopsy, they specifically noted the presence of inflammation, necrosis, fiber splitting, and vacuolar changes. Positive and negative predictive values (PPV and NPV, respectively) were calculated for EMG findings with respect to each pathologic change. PPV was defined as the likelihood that an abnormal finding on EMG would predict a specific pathologic finding on biopsy, and NPV was defined as the likelihood that the absence of an EMG finding would predict the absence of a pathologic finding on biopsy.

Among 224 charts reviewed, six were excluded, as their EMG did not precede their biopsy, leaving 218 patients, 109 each male and female, with a mean age of 54.4 years, for analysis. Of these, 178 (82%) were thought to have EMG findings consistent with myopathy, which was confirmed following biopsy in 143 (80.3%), including 60 with inflammatory myopathy, 18 with muscular dystrophy, eight with congenital myopathy, two with mitochondrial myopathy, 36 with no specific etiology, and 19 miscellaneous.

Among the 35 patients with EMG findings suggestive of myopathy but not confirmed on biopsy, diagnoses included hyperCKemia, denervation atrophy, motor neuron disease, neuromuscular junctionopathy, Guillain-Barré syndrome, polyradiculopathy, other neurogenic process, and no final confirmed diagnosis. EMG sensitivity for a confirmed diagnosis of myopathy was 95.3%, with a specificity of 48.5%.

Short duration motor unit potentials were highly sensitive for myopathy but not specific for any particular pathologic change, whereas myotonic discharges were specific, but not sensitive, for pathologic change. Fibrillation potentials were indicative of inflammation, fiber necrosis, splitting, or vacuolar change, with a sensitivity of 65-74% and a specificity of 58-81%, regardless of the presence of short-duration motor unit potentials. Short motor unit potentials and fibrillation potentials had high NPV for inflammation, fiber type splitting, and vacuolar change, whereas PPV was low for any specific EMG abnormality.

Among 24 EMG studies reported as normal, five had myopathy on muscle biopsy, including two cases of carnitine palmityl transferase II carriers and one each of muscular dystrophy, McArdle disease, and dermatomyositis. Another five patients with normal EMG were diagnosed after muscle biopsy with alternative diagnoses, including denervation atrophy, remote polio, compartment syndrome, and central sensitization syndrome. In the final 14 with normal EMG, no alternative diagnosis was made.

■ COMMENTARY

In a concomitantly published, almost identical study of 100 patients at Mayo Clinic, Rochester,[1] researchers confirmed and extended the above findings. Fibrillation potentials correlated with atrophic and regenerating fibers, fibers reacting for nonspecific esterase, fibers with congophilic inclusions, and increased endomysial connective tissue. Long-duration motor

unit potentials correlated with fiber-type grouping, while short-duration motor unit potentials correlated with atrophic, necrotic, and regenerating fibers, and increased endomysial connective tissue. Increased phases of motor unit potentials correlated with atrophic fibers, increased endomysial connective tissue, and fibers reacting for non-specific esterase, whereas increased turns correlated with atrophic and regenerating fibers, increased endomysial connective tissue, and target formations. Early recruitment correlated with regenerating fibers, perimysial inflammation, and increased endomysial connective tissue. Further examination of muscle biopsy and EMG correlation should look into the combination of EMG findings predicting specific pathology. ■

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ABSTRACT & COMMENTARY

Clinical Outcomes After Oral Anticoagulant-Associated Intracerebral Hematoma

By Santosh Murthy, MD

Assistant Professor of Neurology, Weill Cornell Medical College

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

SYNOPSIS: In this meta-analysis of multiple observational studies, clinical outcomes after oral anticoagulant-associated intracerebral hematoma were similar for those associated with vitamin K antagonists or the new class of direct oral anticoagulants.

SOURCE: Tsivgoulis G, Wilson D, Katsanos AH, et al. Neuroimaging and clinical outcomes of oral anticoagulant-associated intracerebral hemorrhage. *Ann Neurol* 2018;84:694-704.

About one-fifth of all patients with primary intracerebral hemorrhage (ICH) are related to anticoagulant use. Historically, vitamin K antagonists (VKAs), such as warfarin, once widely accepted as the oral medication of choice, were associated independently with higher admission hematoma volumes, hematoma expansion, higher mortality, and more severe disability compared to patients not on anticoagulant medications. The advent of non-vitamin K antagonist, direct oral anticoagulants (DOACs) has added a new dimension to the field of anticoagulation.

The authors of randomized, clinical trials in patients with atrial fibrillation have demonstrated conclusively that the risk of ICH is significantly lower with DOACs compared to VKAs, while the thromboembolic benefit is similar. However, head-to-head comparisons of ICH outcomes in patients on these medications have yielded conflicting results, given limitations of low power, retrospective design, and mostly single-center data.

Tsivgoulis et al presented an individual patient data meta-analysis in which they compared 219 patients with DOAC-associated ICH with 831 with VKA-related ICHs across seven published, international, observational studies. The primary outcome was 30-day all-cause mortality, while secondary outcomes included clinical ICH severity, hematoma expansion, and functional outcomes at prespecified time points.

The authors showed that DOAC use was associated with milder ICH clinical severity, as evidenced by lower National Institutes of Health Stroke Scale scores and smaller admission hematoma volumes, compared to VKA use. However, there were no differences in 30-day mortality (24.3% vs. 26.5%; hazard ratio, 0.94; 95% confidence interval [CI], 0.67-1.31), functional outcomes between the two groups at hospital discharge (common odds ratio, 0.78; 95% CI, 0.57-1.07), or functional status at three months (common OR, 1.03; 95% CI, 0.75-1.43) after adjusting for potential confounders, such as demographics and clinical and radiological characteristics of ICH.

■ COMMENTARY

This individual patient data meta-analysis highlights important baseline clinical and radiological characteristics of DOAC-ICH compared to VKA-ICH. These results are in stark contrast to those reported in a large retrospective cohort study using the American Heart Association's Get With the Guidelines registry of nearly 150,000 ICH patients, which found that DOAC-ICH had lower inpatient mortality and favorable discharge disposition compared to VKA-ICH. However, the results were not adjusted for baseline clinical and radiological ICH severity, which likely confounded the multivariable analyses. One may surmise that selective inhibition of the extrinsic coagulation pathway and shorter half-life of DOACs confer a pharmacologic advantage over VKAs.

With emerging data tipping the balance in favor of DOACs as the oral anticoagulant medication of choice, studies with longer follow-ups of six months to one year are warranted, since the trajectory for recovery after ICH often is slower than that of ischemic stroke.

Current data suggest that rates of mortality and disability are relatively similar between VKA- and DOAC-associated ICH. Emerging data suggest that DOACs have smaller baseline hematoma volumes. As for the risk of ICH, DOACs appear to have a significantly lower risk compared to VKAs. However, the thromboembolic benefit is similar between the two groups. Although the prothrombin complex concentrates are used widely to reverse coagulopathy associated with warfarin use, specific medications, such as idarucizumab and andexanet, are now available as reversal agents for DOACs. ■

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CME QUESTIONS

1. **In patients with Parkinson's disease, slow-wave activity in non-REM sleep generally declines with progression of the disease.**
   a. True
   b. False
2. **Which of the following statements is *false* about magnetoencephalography (MEG) to scalp electroencephalogram (EEG)?**
   a. MEG provides better spatial resolution than EEG.
   b. EEG requires a larger area of cortical activation to detect spike activity than MEG.
   c. MEG can be distorted by intervening tissues.
   d. MEG records tangential dipoles.
3. **Which of the following statements is true regarding electromyography (EMG) and muscle biopsy?**
   a. Abnormal findings on needle EMG often are associated with a plethora of abnormalities on muscle pathology.
   b. Myotonic discharges are very sensitive, but not specific, for pathologic change.
   c. A normal EMG never is associated with biopsy-proven myopathy.
   d. Denervation atrophy is excluded by a normal EMG.
4. **A 69-year-old male diagnosed with new onset paroxysmal atrial fibrillation presents to your clinic for a second opinion regarding choice of anticoagulation between direct oral anticoagulants (DOACs) and vitamin K antagonists (VKAs). Which of the following statements is true?**
   a. DOACs and VKAs have a similar risk of intracerebral hemorrhage (ICH).
   b. DOACs are inferior to VKAs in preventing incident thromboembolic events.
   c. ICH associated with DOAC use has similar mortality and disability compared to ICH resulting from VKA use.
   d. Specific medications to reverse coagulopathy are available for VKAs but not DOACs.

[IN FUTURE ISSUES]

Update on Migraine