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Neurology [ALERT®]

Evidence-based summaries of the latest clinical neurology research

ABSTRACT & COMMENTARY

Polyneuropathy in the Metabolic Syndrome

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: The metabolic syndrome, independent of the diagnosis of diabetes, is associated with the development of polyneuropathy.

SOURCE: Hanewinckel R, Drenthen J, Ligthart S, et al. Metabolic syndrome is related to polyneuropathy and impaired peripheral nerve function: A prospective population-based cohort study. *J Neurol Neurosurg Psychiatry* 2016;87:1336-1342.

Updated by the International Diabetes Federation in 2006, criteria for diagnosing metabolic syndrome includes central obesity based on waist circumference in addition to abnormalities in two of the following: triglycerides, (> 150 mg/dL), high-density lipoprotein cholesterol (HDL-C; < 40 mg/dL for men or < 50 mg/dL for women), blood pressure (systolic ≥ 130, diastolic ≥ 85), and fasting plasma glucose (≥ 100 mg/dL). Elevated fasting glucose and impaired glucose tolerance may increase the risk of polyneuropathy in prediabetes. What role, if any, apart from diabetes or prediabetes, does metabolic syndrome play as a risk factor for polyneuropathy?

Incorporated as part of the Rotterdam Study, a prospective, population-based cohort study, initiated in 1990 of all inhabitants ≥ 55 years of age living in the Ommoord district of Rotterdam, the Netherlands, and expanded in 2006 to include all persons ≥ 45 years of age, a polyneuropathy screen was implemented in June 2013, and the current study included patients enrolled up to October 2015. Among 1,544 persons screened for polyneuropathy, 262 were excluded for logistical reasons, with 1,256 of the remaining 1,310 lacking adequate information to be included in this analysis. Metabolic syndrome was diagnosed based on any three of the following five criteria: increased waist circumference (≥ 94 cm for males, ≥ 80 cm for females), elevated triglycerides, reduced HDL-C (< 39 mg/dL in males, < 50 mg/dL in females, or specific treatment for reduced HDL-C), elevated blood pressure, and elevated fasting glucose (≥ 216

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mg/dL, or use of glucose-lowering medication). Neuropathy screening included a symptom questionnaire, neurological examination, and nerve conduction studies of the sural sensory nerves bilaterally and a unilateral peroneal motor nerve. Statistical analysis included logistic and linear regression analyses, adjusted for age, gender, and height, and splines regression for continuous glucose levels.

Among 1,256 subjects, 45.5% male (n = 571) and 54.5% female (n = 685), with mean age of 70 years, type 2 diabetes was present in 13.9%, impaired fasting glucose in 12.2%, and metabolic syndrome in 52.5% (n = 659). Definite polyneuropathy was present in 5.1% (n = 64); probable polyneuropathy in 7.3% (n = 92), diagnosed by the presence of two abnormal elements on nerve conduction studies; and possible polyneuropathy in 17.4% (n = 218), diagnosed by the presence of one abnormal or two slightly abnormal elements on nerve conduction studies. Regardless of gender, metabolic syndrome was associated with definite polyneuropathy (odds ratio, 1.92; 95% confidence interval, 1.09-3.38), particularly in those individuals who had increased waist circumference and elevated triglycerides, regardless of the presence of diabetes. Diabetes, but not impaired fasting glucose, also was strongly associated with polyneuropathy.

■ COMMENTARY

Polyneuropathy affects 2-7% of the population and is idiopathic in at least 30% of patients. Diabetes, both type 1 and 2, is the most common known cause, and although rigorous glucose control significantly reduces the incidence of neuropathy in type 1 diabetes, it does not have the same effect in type 2, implying that factors other than blood glucose are causative. Evidence now supports the notion that components of metabolic syndrome may be responsible, and efforts to address these may positively affect the incidence of neuropathy, not only in diabetes but in non-diabetic obese individuals as well. ■

ABSTRACT & COMMENTARY

Imaging of Glial Cell Activation in the Brains of Professional Football Players

By Karishma Parikh, MD, and Barry Kosofsky, MD, PhD

Dr. Parikh is Pediatric Resident at SUNY Downstate Medical Center, New York.

Dr. Kosofsky is Professor of Pediatrics and Professor of Neurology and Neuroscience at Weill Cornell Medical College.

Dr. Parikh and Dr. Kosofsky report no financial relationships relevant to this field of study.

SYNOPSIS: In this case-controlled study, PET scanning reflective of microglial activation and diffusion-tensor imaging assessing white matter integrity was performed on 14 National Football League players (four current, 10 retired) and compared to 16 matched controls, suggesting significant ongoing localized brain injury and repair along with subtle white matter changes in professional football players.

SOURCE: Coughlin JM, Wang Y, Minn I, et al. Imaging of glial cell activation and white matter integrity in brains of active and recently retired National Football League players. *JAMA Neurol* 2016; Nov 28. doi: 10.1001/jamaneurol.2016.3764. [Epub ahead of print].

There has been tremendous clinical and public interest in identifying the long-term consequences of concussion on brain structure and function, and the possible relationship between repetitive concussive or sub-concussive head injury in contributing to the subsequent development of chronic traumatic encephalopathy (CTE). To address this question, Coughlin et al pioneered the use of high-resolution positron-emission tomographic (PET) imaging using a second-

generation TPSO-targeted radiotracer, [^{11}C]DPA-713, an indirect reflection of microglial activation, serving as a functional biomarker of ongoing brain injury and repair following concussion. Using this in vivo brain imaging approach, they found TPSO to be persistently activated in multiple temporal lobe and adjacent brain regions, despite a mean of seven years since the last self-reported concussion. Using diffusion tensor imaging (DTI) and structural MRI imaging, they additionally identified subtle alterations in white matter integrity in former NFL players compared to matched control participants.

Four active NFL players along with 10 former NFL players (defined as stopping play within the last 12 years) were recruited for this study, along with 16 control men matched for age, education, and body mass index. In addition to PET imaging and MRI, a board-certified psychiatrist performed clinical and neuropsychological testing on all participants.

There was no significant difference in clinical and demographic characteristics nor in neuropsychological performance between the NFL players and control participants.

For brain PET analysis, 12 regions of interest were selected for study: right and left hippocampus, parahippocampus, entorhinal cortex, amygdala, temporal pole, and supramarginal gyrus. FreeSurfer, an automated morphometric image analysis pipeline, was used to quantitate total cortical gray matter and total intracranial volume, data used to determine the total distribution volume (V_T) of TPSO for each of these areas, using a two-way ANOVA, with cohort (NFL players vs. controls) and genetic group (polymorphisms coding for high vs. low TPSO binding affinities) as independent fixed factors.

DTI data were analyzed utilizing an automated white matter segmentation and 3D analytic pipeline calculating both fractional anisotropy (FA) and mean diffusivity (MD) values. They studied eight predefined long cortical-subcortical white matter projection pathways hypothesized to be vulnerable to inertial brain injury: the right and left anterior, superior, and posterior corona radiata, and posterior thalamic radiation. Statistical analyses for both the morphometric and diffusion tensor data utilized a Bonferroni correction.

Participants assessed and analyzed on T1-weighted brain MRI showed no structural abnormalities and no between-group volumetric abnormalities. The V_T of TPSO was significantly elevated in the 12 NFL players as compared with 11 control participants in eight of the 12 areas analyzed, including the left and right hippocampus, left entorhinal cortex, left and right parahippocampal cortex, left and right supramarginal gyrus, and left temporal pole. There was no effect of age, race, ethnicity, body mass index, or years of education affecting these between-group differences in V_T of cortical gray matter. Among the NFL players, there was no significant difference in V_T of cortical gray matter seen between the active and former players, nor was there an effect of years in the NFL, number of NFL games played, or number, age of first, or years since last self-reported concussion.

In NFL players, DTI analyses revealed a lower FA, a potential indicator for decreased white matter integrity, in only one of the eight areas analyzed: the right posterior thalamic radiation. MD values, often found to demonstrate the inverse relationship of FA values, were higher in NFL players in only one of the eight areas analyzed: the left anterior corona radiata.

■ COMMENTARY

This study identifies the value of in vivo high resolution PET imaging utilizing a novel radiotracer, [^{11}C] DPA-713, to indirectly demonstrate evidence for the persistent activation of microglia in the brains of NFL players as compared with controls. In these same subjects, DTI revealed minimal between-group differences, and neither morphometric nor neuropsychologic measures distinguished the two groups. This study provides a proof of principle for research identifying the role of microglia in activating responses in the brain following injury and during recovery, and the application of this method to study the long-term effects of concussion. Regarding the former, although PET imaging with [^{11}C]DPA-713 is an indirect measure of microglial activation following TBI, the results reported confirm data from preclinical studies suggesting significant and ongoing changes mediated by microglial activation occur for months to years following concussive brain injury. Although it will be essential to clarify whether such changes in microglial activation are adaptive or maladaptive, this method may provide an essential starting point for clinico-neuroanatomic correlations. Regarding the latter, if validated, this method may be useful as an early functional biomarker of significant traumatic brain injury, which may be evident in the absence of structural changes, or neuropsychologic deficits. Such validation will require larger, well-controlled, longitudinal analyses, which if confirmed, could set the stage for therapeutic trials to try to prevent some of the long-term consequences of traumatic brain injury, potentially including CTE in NFL players. ■

ABSTRACT & COMMENTARY

Does Therapeutic Hypothermia Improve Functional Outcomes After Convulsive Status Epilepticus?

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 multicenter trial in France, patients admitted to the ICU from 2011-2015 for convulsive status epilepticus were randomly assigned to receive standard therapy (control group) or hypothermia plus standard therapy (treatment group). The primary outcome measure was an absence of functional impairment at 90 days after seizure onset, as measured by the Glasgow Outcome Scale (score of 5). There was no significant difference in outcomes between the two groups.

SOURCE: Legriel S, Lemiale V, Schenck M, et al. Hypothermia for neuroprotection in convulsive status epilepticus. *N Engl J Med* 2016;375:2457-2467.

Convulsive status epilepticus (CSE) is considered a neurological emergency, and even when treatment with antiepileptic drugs is initiated early, in-hospital mortality can be as high as 20% and as high as 40% when it remains medically refractory.[1] In addition, a prospective study by the same lead author showed that about half of survivors had "severe" residual functional impairment 90 days after symptom onset.[2] As such, the authors proposed combining therapeutic hypothermia to standard treatment for CSE to see if this had added neuroprotective and antiepileptic benefits, leading to an absence of later functional impairment.

[The findings of this trial do not support the addition of therapeutic hypothermia to standard medical treatment for convulsive status epilepticus in critically ill patients.]

This study was a multicenter, randomized, controlled trial conducted in 11 French ICUs from March 2011 to January 2015. All patients were adults admitted to an ICU for less than eight hours since onset of CSE and were mechanically ventilated. CSE was defined as five minutes or more of continuous clinical seizure activity or more than two clinical seizures without return to baseline in between. Patients (n = 268) were randomized to receive either standard medical therapy alone (control group, n = 130) or hypothermia plus standard therapy (treatment group, n = 138). In the hypothermia group, the goal was to lower core body temperature, as measured by an esophageal probe, to 32-34°C and to maintain this for 24 hours. This was achieved through cold IV fluids, and maintained with ice packs at the groin and neck and with a cold air tunnel around the body. Patients in this group were sedated with propofol and neuromuscular blockade, and patients in the control group requiring sedation also were given propofol using a similar protocol. Continuous EEG monitoring was also initiated for both groups within two hours after randomization and maintained for at least 48 hours or until the hypothermia group was normothermic. A 30-minute segment of the initial two hours of EEG was read at a central site to determine the presence of ongoing seizure activity (i.e., whether a patient was refractory) and used to decide the need for a burst-suppression pattern.

The groups were similar in terms of demographics and clinical characteristics. The median age was 57 years and 65% were men. Nearly half (49%) had a history of epilepsy, with most episodes of CSE starting outside of the hospital (65%). Median time from seizure onset to initiation of drug therapy was 40 minutes, and it required a median of two medications before seizures were controlled. The median time to control electrical seizure activity was 80 minutes, although SE was refractory in 25% at the time of randomization. In the hypothermia group, cooling was initiated a median of 5.8 hours after seizure onset and the target temperature was reached in 98% of patients within a median of 5.2 hours.

The primary outcome was an absence of functional

impairment at 90 days as measured by a score of 5 on the Glasgow Outcome Scale (GOS), indicating little to no impairment. They found that 49% of patients in the hypothermia group vs. 43% of those in the control group achieved a score of 5, which was not significantly different. However, it was noted that the odds ratio for recovery was significantly higher in patients who were ≤ 65 years of age when comparing the treatment vs. control groups (1.75) as compared to older patients (0.49). In terms of secondary outcomes, there were no significant differences in mortality rates between the groups, although significantly more patients in the control group were found to progress to electrographic SE (29 vs. 15). Lastly, more adverse events were noted in the hypothermia (85%) vs. control group (77%), with the majority of these being aspiration pneumonia in both groups.

■ COMMENTARY

The findings of this trial do not support the addition of therapeutic hypothermia to standard medical treatment for CSE in critically ill patients. However, there were several limitations with this study. First, the median time for electrographic seizure control was 80 minutes, yet the hypothermia protocol was not initiated until a median of 5.8 hours after seizure onset and the goal temperature was achieved a median time of an additional 5.2 hours later. This protocol may have been better used in patients who were refractory; it may not have been necessary in patients whose seizures resolved with medical treatment alone. In addition, the delay in initiating hypothermia may make this a less practical choice for SE, as prolonged seizures can lead to failure of intrinsic inhibitory mechanisms[3] and may result in refractory CSE. However, the authors did note that more patients in the control group had refractory or super-refractory SE, although this was not significant and did not seem to affect overall outcome. Given the differences in age, future directions could focus on use of therapeutic hypothermia in younger patients (< 65 years of age), initiated earlier after seizure onset, and with more refractory cases. ■

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ABSTRACT & COMMENTARY

Ambulatory Autonomic Testing in Multiple System Atrophy and Parkinson's Disease

By Claire Henchcliffe, MD, PhD

Associate Professor of Neurology and Neuroscience, Weill Cornell Medical College

Dr. Henchcliffe reports she is a consultant and on the speakers bureau for Acadia Pharmaceuticals, Impax Pharmaceuticals, and Allergan, and is a consultant for US WorldMeds and Gerson Lehman Group.

SYNOPSIS: A comparison of ambulatory blood pressure monitoring with tilt-table testing in 23 patients with multiple system atrophy, 18 with Parkinson's disease and autonomic dysfunction, and 33 with Parkinson's disease alone demonstrated 82% sensitivity and 100% specificity in detecting orthostatic hypotension. This suggests ambulatory monitoring provides valuable information on these patients' function.

SOURCE: Vichayanrat E, Low DA, Iodice V, et al. Twenty-four-hour ambulatory blood pressure and heart rate profiles in diagnosing orthostatic hypotension in Parkinson's disease and multiple system atrophy. *Eur J Neurol* 2017;24: 90-97.

This observational study included patients referred to a specialist autonomic testing unit for evaluation of orthostatic symptoms from 2004-2013. The patients enrolled comprised three groups: multiple system atrophy (MSA); Parkinson's disease with autonomic failure (PDAF), in whom autonomic failure was defined on the basis of blood pressure (BP) and heart rate (HR) responses to orthostasis, Valsalva, and deep breathing; and Parkinson's disease without autonomic failure (PD). A total of 74 patients were included (MSA: 23; PDAF: 18; PD: 33). Mean age was higher in the PDAF group (72 ± 7 years vs. 62 ± 9 years for MSA and 64 ± 10 years for PD; $P < 0.05$). Median disease duration (IQR: inter-quartile range) was 4 (3-6) years, 7 (4-10) years, and 6 (2-10) years for the MSA, PDAF, and PD groups, respectively. All patients underwent tilt-table testing with BP and HR recording while off anti-PD medication. For comparison, each was then fitted with an ambulatory BP monitoring (ABPM) device, that provided BP and HR measures every 20 minutes during the day and every 60

minutes at night for a 24-hour period. Furthermore, patients performed a five-minute standing test at four pre-specified times during the day. Diaries were also completed, recording symptoms and activities. ABPM was able to detect orthostatic hypotension (≥ 20 mm systolic BP drop during the standing tests) with 82% sensitivity and 100% specificity compared to the "gold standard" tilt-table testing. Diastolic BP measures performed less well, with sensitivity and specificity of 57% and 94%, respectively, when comparing ABPM to tilt testing. In contrast to tilt-table testing, ABPM provided a longer period of monitoring, including information on circadian patterns in each group. Although the normal pattern is a nighttime "dip" in BP, abnormal BP circadian rhythm was noted in all 96% MSA, 78% PDAF, and 48% PD. Of these, 57% MSA, 56% PDAF, and 15% PD demonstrated a reversed circadian BP pattern.

■ COMMENTARY

BP management of individuals with PD and MSA in the clinic is often challenging. BP control is affected not only by the disease process itself, but also by dopaminergic medications, comorbidities in a generally older population, and many of the drugs taken to manage those comorbidities. Vichayanrat et al attempted to minimize the effects of medications and comorbidities using careful inclusion/exclusion criteria. In practical terms, the study suggests that diagnosing orthostatic hypotension by ambulatory monitoring is highly accurate when compared with in-clinic tilt testing. Orthostatic hypotension is under-recognized in PD, and may present with non-specific or unexpected complaints such as a "coat hanger" pain. Therefore, broader use of this relatively straightforward testing modality could improve patient care. Moreover, the study provides a valuable description of cardiac autonomic dysfunction in MSA and PD/PDAF, albeit in a small number of clinically diagnosed individuals. It highlights how fairly simple ambulatory monitoring can significantly augment information from the clinic, particularly in a situation in which motivated subjects will follow a stand-testing protocol and complete diaries.

However, the report raises some questions. It is unclear whether feasibility and level of accuracy will be matched in the neurology clinic, as opposed to an academic center with highly motivated patients with specialist referrals. There is no information on other forms of autonomic function, nor a description of other clinical features associated with the three categories of patients. And although the authors discussed mechanism and possible involvement of the hypothalamic suprachiasmatic nucleus, lack of information on sleep disruption, level of physical activity, and other factors make this highly speculative. Finally, use of continuous monitoring outside of the clinic may augment the "snapshot" of traditional in-clinic evaluation. Establishing how well such monitoring performs in regular clinical care will take more work, but in the meantime ABPM may be considered to support diagnosing and treating important non-motor manifestations of PD and MSA. ■

ABSTRACT & COMMENTARY

Migraine: Differences Between Males and Females

By Dara Jamieson, MD

Associate Professor of Clinical Neurology, Weill Cornell Medical College

Dr. Jamieson reports she is a consultant for Bayer and Boehringer-Ingelheim.

SYNOPSIS: Hormonal and genetic differences factor into a greater prevalence and disability burden of migraine in teenaged girls and women; however, migraine is underdiagnosed and inadequately treated in boys and men.

SOURCE: Vetvik KG, MacGregor EA. Sex differences in the epidemiology, clinical features, and pathophysiology of migraine. *Lancet Neurol* 2017;16:76-87.

Migraine is more prevalent in women, who are more likely to seek medical help for their headaches and to participate in clinical trials, as compared to similarly affected men. However, men with migraine may be underdiagnosed or misdiagnosed and, therefore, inappropriately treated. This review outlined the sex differences in epidemiology, clinical features, and pathophysiology in this female-predominant, but male-afflicting, primary headache disorder. Although data from the Global Burden of Disease Study 2015 found that migraine is two to three times more prevalent in adult women than in men, migraine is equally likely to occur in both sexes prior to puberty. Age-specific prevalence

of migraine, both without and with aura, peaks at a younger age in boys than in girls. Then, girls in their teens develop migraines more frequently than do teenaged boys. Migraine incidence peaks in the late teens in boys at 6.2 cases per 1,000 human-years and in their early 20s in women at 18.2 cases per 1,000 human-years. The rate of increase in migraine prevalence is dramatically higher in women in their late teens and young adulthood than it is in similarly aged men, who are more likely to have longer-lasting periods of migraine remission after childhood.

Clinical features of migraine appear to be relatively similar in men and women, although women report longer duration of attacks. Migraine with aura, in about 8% of women and 4% of men, occurs in the same ratio in both sexes as does the twice-as-prevalent migraine without aura. Disability associated with migraine is greater in women (fourth leading cause of years lived with disability, according to the Global Burden of Disease Study 2015) than in men (eighth leading cause), possibly related to longer duration of attacks and higher relapse rates, in combination with multiple household, childcare, and employment responsibilities for women. Despite migraine's comorbidity with medical and psychiatric disorders, there is no consistent sex difference in comorbid conditions. The known data on the link between migraine with aura and stroke are based on observational studies with female predominance, thus limiting the analysis of sex differences.

The treatment difference found between men and women, with women more likely to use prescription acute pain and preventative medications, likely reflects their greater likelihood to seek professional consultation for their migraine disorder. Men and women appear to have similar responses to triptans and to medications used preventively.

Migraine is a polygenetic disorder with variable transmission and a strong influence from environmental and hormonal factors. Clinical features of migraine in women emphasize the role of female sex hormones in migraine triggering. Migraine without aura is associated with estrogen withdrawal leading to menstrual migraine, which are symptomatically more disabling than non-menstrual migraine. Later stages of pregnancy are often a time of relief from migraine without aura. However, high estrogen states, including with exogenous estrogen, may be associated with an increase in migraine with aura. Perimenopausal and menopausal fluctuations in estrogen levels caused increased migraine, until postmenopausal hormone stabilization leads to migraine improvement. The prevalence of migraine in male to female transgender people is similar to the prevalence in genetic females. Little is known about the role of testosterone in migraine, although the hormone may have anti-nociceptive and anti-inflammatory properties.

■ COMMENTARY

The most important theme from this comprehensive and well-written review of sex differences in migraine is that boys and men deserve attention. About 43% of women have a migraine in their lifetime and the majority of their headaches are appropriately diagnosed and treated. About 18% of men have a migraine in their lifetime and the majority of their headaches are misdiagnosed and undertreated. The authors emphasized that, "[t]he under-diagnosis of migraine in men is likely to result in suboptimal management and less participation in clinical trials." Males, from boyhood to adulthood with migraine, are not going to get relief from migraine pain and the associated symptoms until they seek help from knowledgeable physicians who recognize the variability in the presentation of migraine, make the correct diagnosis, and offer appropriate and effective advice for lifestyle management and use of prescription medication. There may be stigma associated with "a women's disorder" so that the misdiagnoses of "chronic sinus," "recurrent sinus infections," or "tension headache" may be made in boys and men with migraine, if headaches as a medical complaint are even addressed at all. Sinus surgery, antibiotics, opiates, barbiturates, and the frequent use of over-the-counter medications are not appropriate treatments for migraine in males or females. Discussions of trigger recognition and preventive lifestyle modification are not initiated if male migraine is not recognized. Triptans, which are of life-changing benefit to millions of migraine sufferers, should be prescribed for boys and men with migraine. Given the significant effect of frequent migraine on quality of life, prescription preventive treatments should be discussed with every male migraine sufferer. Boys and men with migraine deserve to be treated with the same care and respect that are accorded to girls and women. ■

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CME QUESTIONS

1. **Which of the following is true regarding metabolic syndrome?**
   a. It is associated with definite polyneuropathy regardless of the presence of diabetes.
   b. It is associated with definite polyneuropathy only in the presence of diabetes.
   c. It is associated with definite polyneuropathy only in the presence of diabetes in obese individuals.
   d. It is associated with definite polyneuropathy only in diabetic individuals with elevated triglycerides.

2. **Which of the following statements is false regarding brain imaging in professional football players?**
   a. In symptom-free NFL players, structural T-1 MRI studies are normal.
   b. Neuropsychological assessments in NFL players are not significantly different than in matched controls.
   c. The number of self-reported concussions does not influence the results of PET imaging.
   d. Abnormal PET imaging for microglial activation predicts the development of chronic traumatic encephalopathy.

3. **What was the primary outcome measure for the study on therapeutic hypothermia in convulsive status epilepticus?**
   a. Control of seizures in the first 30 minutes on continuous EEG
   b. Mortality rate
   c. Incidence of adverse events
   d. Absence of functional impairment at 90 days after seizure onset

4. **Which of the following is correct about blood pressure control in Parkinson's diseazse (PD) and multiple system atrophy (MSA)?**
   a. Orthostatic hypotension only occurs in MSA and not PD.
   b. Tilt-table testing is the only objective means of diagnosing orthostatic hypotension in PD and MSA.
   c. Patients with PD and MSA may manifest orthostatic hypotension but circadian changes in BP are normal.
   d. BP in patients with MSA and PD may have a reversed circadian rhythm.

5. **Which of the following statements is true regarding migraine?**
   a. Migraine incidence peaks at a younger age in boys than in girls.
   b. Men with migraine are more likely to have aura with their headaches, than are women.
   c. Menstrual migraine is more likely to be associated with aura, than is non-menstrual migraine.
   d. Migraineurs without aura have a greater stroke risk than non-migraineurs.

[IN FUTURE ISSUES]

Advances in Multiple Sclerosis Treatments