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Neurology [ALERT®]

Evidence-based summaries of the latest clinical neurology research

ABSTRACT & COMMENTARY

Impulse Control Disorders in Parkinson's: Are All Dopamine Agonists Equal Offenders?

By Claire Henchcliffe, MD, PhD

Associate Professor of Neurology and Neuroscience, Weill Cornell Medical College

Dr. Henchcliffe reports she is on the speakers bureau and advisory boards for Teva, IMPAX, and ACADIA; is on the advisory board for U.S. World Meds; and is a consultant for Cynapsus and Pfizer.

SYNOPSIS: This observational study of 425 patients with a broad range of stages of Parkinson's disease found that long-acting pramipexole and transdermal rotigotine were less likely to be associated with impulse control disorders than were immediate-release pramipexole and any formulation of ropinirole. This study highlights differences between dopamine agonists that may affect patient care.

SOURCE: Rizos A, Sauerbier A, Antonini A, et al. A European multicentre survey of impulse control behaviours in Parkinson's disease patients treated with short- and long-acting dopamine agonists. *Eur J Neurol* 2016;23:1255-1261.

This observational study used retrospective and prospective data collection, with chart review and interviews, for patients with Parkinson's disease (PD) to determine the occurrence of impulse control disorders (ICDs) in the context of dopamine agonist treatment. Specifically, the investigators focused on whether immediate-release formulations (pramipexole IR and ropinirole IR) would be associated with ICDs differently than long-acting formulations (pramipexole ER, ropinirole XL, rotigotine transdermal patch). Data were collected from charts of 425 PD patients who either were already taking or were starting dopamine agonist therapy, in eight European specialist centers over a three-year period of routine clinical care. Ascertainment of ICD was made by direct inquiry during clinic visits and, in part, by answers to specific questions on the non-motor rating scale. The cohort comprised 61% men, with mean age 68.3 (range 37-90) years, mean age of PD onset 61 (range 18-85) years, and mean disease duration 7.5 (range 0-37) years. Of the long-acting agonists, 43.1% of patients took rotigotine, 38.8% took ropinirole XL, and 17.9% took pramipexole ER. Of the short-acting agonists, 24.7% of patients took prami-

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pexole IR and 10.1% took ropinirole XL. Overall, ICDs that were deemed clinically relevant were present in 13.4%, and this group of patients were slightly more likely to be men (79%) and have a younger age of onset (55.7 years). Interestingly, the percentages of ICDs varied quite markedly between agonists. In those using rotigotine, ICDs were only reported in 4.9%; in those using pramipexole, ICDs were reported in 6.6% for long-acting (ER) vs. 19% for short-acting (IR). However, for those using ropinirole, ICDs were similar for both formulations (13.9% and 14% for XL and IR, respectively). Only about half of these patients discontinued dopamine agonists, but how many reduced the dose is unclear. Curiously, of the ICDs reported (binge eating, gambling, hypersexuality, multiple), results suggest binge eating much more commonly in pramipexole IR than in ropinirole IR and XL, and hypersexuality more commonly with ropinirole (IR and XL).

■ COMMENTARY

The occurrence of ICDs associated with PD medications, and with dopamine agonists in particular, long has been a source of concern, with a seminal publication on pathological gambling in 11 subjects in 2005.[1] Although ICDs initially were thought to be rare, in 2010, the DOMINION study of 3,090 PD patients in North America found that use of a dopamine agonist was associated with a 2- to 3.5-fold increase in risk of ICD, and that 17.1% of patients taking dopamine agonists suffered from at least one ICD. Given the potential and well-reported consequences of ICDs, this has contributed to a reluctance in some cases to use these drugs. Moreover, a "withdrawal syndrome" also has been described in some patients as agonists are stopped because of side effects, including ICDs. This creates difficulty in the clinic because despite established benefits, it is not easy to predict who is at risk of ICDs. Therefore, this study by Rizos and colleagues is a welcome step toward teasing out the complexity of dopamine agonist effects, and follows from another recent report that rotigotine is associated with a lower risk of ICDs than other agonists. However, the study leaves many questions unanswered. There is very little information on what happened to patients over time, although from the numbers reported, it seems many must have tried multiple agonists and also different doses at different times. This means the doses reported as taken are hard to interpret. Other medications, and their potential contributions, are represented as levodopa equivalents, but differences between groups are not discussed. A major drawback, as acknowledged by the investigators, is the lack of a formal screening tool (such as the Questionnaire for Impulsive-Compulsive Disorders, or QUIP) to detect ICDs in this study. However, one would imagine that any resulting underestimate of ICDs should apply across the board. Some of these investigators have suggested previously that long-acting formulations be considered as an alternative for those experiencing ICDs on short-acting agonists. Currently, there are too little data to have a high degree of confidence in that approach, and current advice remains to reduce and/or eliminate the dopamine agonist in cases of troublesome ICDs. However, if further studies support the notion that rotigotine and pramipexole ER are safer for patients from the point of view of ICDs, this will be cause for a change in practice. ■

REFERENCE

1. Dodd ML, Klos KJ, Bower JH, et al. Pathological gambling caused by drugs used to treat Parkinson disease. *Arch Neurol* 2005;62:1377-1381.

ABSTRACT & COMMENTARY

Neuropathy in Myeloma

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: Peripheral neuropathy is uncommon at presentation in patients with myeloma, and may be complicated by vitamin D deficiency and the neurotoxic effects of chemotherapy.

SOURCE: Leone C, Federico V, La Cesa S, et al. An observational study assessing peripheral neuropathy related to multiple myeloma. *Neurol Sci* 2016;37:1141-1143.

Lumbosacral and thoracic radiculopathies are the most common neurologic complications of multiple myeloma, resulting from compression of nerve roots by collapsed bone or paravertebral plasmacytoma. Approximately 5% of patients experience spinal cord compression, a neurologic emergency, usually from vertebral body fracture with resultant bone fragment extrusion or from extramedullary plasmacytoma. Peripheral neuropathy is uncommon in multiple myeloma, except in those with POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes), and usually is due to amyloidosis. What is the prevalence of peripheral neuropathy in newly diagnosed, untreated patients with multiple myeloma?

To address this question, 180 newly diagnosed multiple myeloma patients seen at the Hematology Department, Sapienza University, Rome, between March 2006 and December 2014, were evaluated by the Department of Neurology. Patients were excluded if they had any preexisting condition associated with neuropathy, including diabetes, alcoholism, prior cancer, hepatitis C virus, or vitamin deficiency, leaving 153 patients for study. All patients underwent a thorough neurologic history, including questioning regarding dysautonomia and DN4 questionnaire for distinguishing nociceptive and neuropathic pain, and complete neurologic examination with careful attention to the sensory components. Standard sensory and motor nerve conduction studies were performed on all patients, encompassing the sural, ulnar, and radial sensory nerves, and peroneal, tibial, and ulnar motor nerves, with the median nerve omitted because of the high prevalence of incidental carpal tunnel syndrome in the general population. Additionally, skin punch biopsy, 10 cm proximal to the lateral malleolus, was performed on patients with distal paresthesiae but normal nerve conduction studies. Primary outcome measures for defining peripheral neuropathy required symptoms consistent with neuropathy in conjunction with abnormal nerve conduction studies, or, where nerve conduction studies were normal, skin biopsy abnormalities to diagnose small fiber neuropathy. Statistical analysis comprised the Mann-Whitney and Fisher's exact tests, with $P < 0.05$ considered statistically significant.

Peripheral neuropathy was found in 7.2% (n = 11), was equally distributed between men and women, was more frequent in older patients (68.7 years vs. 63.2 years), and was large fiber in all but one, who had pure small fiber neuropathy. Negative symptomatology, sensory hypesthesia in the feet, was predominant, with absent Achilles' deep tendon reflexes and decreased sural sensory nerve action potential amplitudes on electrodiagnostic studies. Motor compound muscle action potential amplitudes were spared in all, despite the occasional presence of very mild extensor digitorum brevis weakness on examination. Neuropathy at time of myeloma diagnosis is uncommon, but raises the possibility that these patients may be at greater risk of developing chemotherapy-induced neuropathy as treatment is initiated.

■ COMMENTARY

In a non-randomized, six-center study across the United States, encompassing 111 multiple myeloma patients treated with bortezomib or thalidomide for at least 12 weeks, symptoms of peripheral neuropathy were present in 58%, and vitamin D levels were found to be deficient (< 20 ng/mL) or insufficient (20-29.9 ng/mL) in 42%. Although vitamin D levels among these patients were similar to those found in the general adult population and no correlation was evident between vitamin D levels and neuropathy, sensory and motor peripheral neuropathy was more severe in vitamin D-deficient patients, and sensory peripheral neuropathy was more severe in vitamin D-insufficient patients. Low vitamin D levels are associated with more severe neuropathy in myeloma patients and should be monitored and supplemented where necessary.[1] ■

REFERENCE

1. Wang J, Udd KA, Vidisheva A, et al. Low serum vitamin D occurs commonly among multiple myeloma patients treated with bortezomib and/or thalidomide and is associated with severe neuropathy. *Support Care Cancer* 2016;24;3105-3110.

ABSTRACT AND COMMENTARY

Association of Traumatic Brain Injury with Late-life Neurodegenerative Diseases

By Nitin K. Sethi, MD

Associate Professor of Neurology, Weill Cornell Medical College

Dr. Sethi reports no financial disclosures relevant to this field of study.

SYNOPSIS: This study analyzed pooled clinical and neuropathological data of older adults free of dementia from three prospective cohort studies and found that traumatic brain injury with loss of consciousness was associated with risk for Lewy body accumulation, Parkinson's disease, and progression of Parkinsonism, but not dementia, Alzheimer's disease, neuritic plaques, or neurofibrillary tangles.

SOURCE: Crane PK, Gibbons LE, Dams-O'Connor K, et al. Association of traumatic brain injury with late-life neurodegenerative conditions and neuropathologic findings. *JAMA Neurol* 2016; Jul 11. doi: 10.1001/jamaneurol.2016.1948. [Epub ahead of print].

Traumatic brain injuries (TBI) are common and occur both in the civilian and military setting. Short- and long-term sequelae of TBI include motor and sensory deficits as well as neuropsychiatric disorders. There is growing concern that repeated TBI, even milder forms (concussion), can lead to chronic traumatic encephalopathy. Concern also has been raised about an increased risk of Alzheimer's disease (AD), Parkinson's disease (PD), and other dementias following TBI. Crane et al pooled clinical and neuropathological data from three prospective cohort studies (Religious Orders Study [ROS], Memory and Aging Project [MAP], and Adult Changes in Thought [ACT] study) to determine whether TBI with loss of consciousness (LOC) was associated with an increased risk for clinical and neuropathological findings of AD, PD, and other dementias. The ROS study enrolled older religious clergy from more than 40 groups across the United States; MAP enrolled older residents from Chicago-area retirement facilities and subsidized housing, church groups, and social service agencies; and ACT enrolled older Seattle-area Group Health members. Of 7,130 participants (2,879 [40%] men; overall mean [SD] age, 79.9 years), 865 reported a history of TBI with LOC. In 45,190 person-years of follow up, 1,537 incident cases of dementia and 117 cases of PD were identified. TBI with LOC was not associated with incident dementia or AD. TBI with LOC > 1 hour was associated with incident PD (ACT study). TBI with any LOC was associated with progression of parkinsonian signs (ROS and MAP studies). Neuropathological findings revealed an association of TBI with the presence of Lewy bodies (either in the substantia nigra and/or locus ceruleus or in the frontal or temporal cortex) and also cortical microinfarcts. The authors did not find associations between TBI with LOC and neurofibrillary degeneration or neuritic plaques. APOE genotype status did not affect the results of the study. Limitations of the study included lack of an ethnically diverse study population and failure to account for potential confounders, such as occupational history, smoking, physical activity, body mass index, risk taking, and alcohol intake.

■ COMMENTARY

Physicians evaluating and treating patients with TBI frequently are asked to predict both short-term and long-term sequelae. The lack of a reliable and reproducible TBI biomarker (serum or CSF) and its association with well-defined clinical and neuropathological measures of outcome makes the task more difficult. Recent studies have raised concern about the association of multiple concussions (mild TBI) with the development of chronic traumatic encephalopathy, especially in young, fit athletes competing in contact sports, such as boxing and football. The effect of TBI with LOC on the aging brain is less well known, with recent studies raising concern for neurodegenerative disorders such as AD, PD, as well as certain psychiatric disorders. Future well-designed studies should assess the association of TBI with LOC against well-defined clinical and neuropathological measures of outcome at different points post-injury. A better understanding of the pathophysiological process and individual traits that increase susceptibility to neurodegenerative diseases following TBI are needed.[1] ■

REFERENCE

1. Young JS, Hobbs JG, Bailes JE. The impact of traumatic brain injury on the aging brain. *Curr Psychiatry Rep* 2016;18:81. doi: 10.1007/s11920-016-0719-9.

ABSTRACT & COMMENTARY

Functional MRI in REM Behavior Disorder Is Suggestive of Future Parkinson's Disease

By Alan Z. Segal, MD

Associate Professor of Clinical Neurology, Weill Cornell Medical College

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

SYNOPSIS: Rapid eye movement behavior disorder carries an increased risk of future Parkinson's disease and has fMRI and DaTSCAN features that are similar to those in patients with Parkinson's disease.

SOURCE: Rolinski M, Griffanti L, Piccini P, et al. Basal ganglia dysfunction in idiopathic REM sleep behavior disorder parallels that in early Parkinson's disease. *Brain* 2016;139:2224-2234.

Rapid eye movement (REM) behavior disorder (RBD) is a syndrome in which patients fail to suppress muscle activity during REM sleep. As a consequence, they act out their dreams. It has been shown that RBD may be a precursor to neurodegenerative disease, specifically the "α-synucleinopathies" — Parkinson's disease (PD), dementia with Lewy bodies, and multiple system atrophy. Therefore, RBD may represent a preclinical state of basal ganglia decline.

Rolinski et al used functional MRI (fMRI) to demonstrate that, when compared to controls, RBD patients show the same pattern of activity as patients who already have early PD. In typical fMRI studies, increased metabolic activity of the brain is observed when a subject is asked to perform a variety of tasks while inside the magnet. The brain "lights up," showing increased BOLD (blood oxygen level dependent) signals in correspondingly activated motor, sensory, visual, and association cortices. In the current study, subjects are passive in the scanner, and a resting state (RS)-fMRI pattern is observed. Using a technique called dynamic causal modeling, a series of spontaneously occurring, slow changes are observed in regions of the brain that are architecturally distinct but have strong functional connectivity. Abnormalities in this connectivity may be detected at rest without the use of any specific activation paradigm.

In PD, the basal ganglia network (BGN) identifies a pattern of activation seen on RS-fMRI that involves the caudate, putamen, pallidum, subthalamic nucleus, and supplementary motor area. The RS-fMRI of the BGN previously has been shown to differentiate PD from controls, with excellent sensitivity and moderate specificity. Interestingly, while RS-fMRI may lack specificity, alternative fMRI techniques (known as seed-based methods) achieve specificity by selecting very specific voxels for analysis. These are distinctly different from RS-fMRI of the BGN, which is a more integrative, widely distributed imaging method.

In this study, RBD patients (n = 26) showed a BGN pattern that was convincingly similar to PD patients (n = 46) and different from controls (n = 23). In fact, while the sensitivity of this pattern for RBD and PD was equal (96% for both), the pattern was slightly more specific for RBD (78%) than it was for PD (74%) in comparison to controls.

The fMRI data in this study were supplemented in a subset of subjects with DaTSCAN imaging (RBD n = 8, PD n = 10, and controls n = 10). DaTSCANs are single photon emission tomography (SPECT) images using the tracer ^{123}I-ioflupane, which has a high affinity for presynaptic dopamine transporters. PD patients showed reduced average DAT uptake values when compared to controls (for example, 2.47 vs. 3.43 in the caudate and 1.86 vs. 3.10 in the putamen). RBD patients fell into an intermediate range (3.19 and 2.69 in the caudate and putamen, respectively), which were above that seen with PD, but below control norms. However, these findings for RBD did not reach statistical significance, likely because of small numbers.

[The connection between rapid eye movement behavior disorder and Parkinson's disease deserves further investigation.]

There have been limited prior studies in RBD using other tracers, such as fluorodopa PET activity as well as 11C dihydrotetrabenazine (11C -DTBZ) — both suggesting loss of dopaminergic neurons. In the current study, using detailed morphometric analysis, neither RBD or PD could be differentiated structurally from controls.

■ COMMENTARY

All of these data suggest that RBD may represent prodromal PD in patients who are completely normal in the waking state. It is challenging to know how to counsel any RBD patient regarding PD risk and, even more challenging, to counsel patients without overt RBD whose only abnormality is the finding of REM sleep without atonia (RSWA) on a polysomnogram (PSG). Such PSG-positive RSWA may manifest either as subtle, but clinically apparent, periodic limb movements in non-REM sleep that continue in REM, or as clinically silent surface EMG muscle activity. Neither of these phenomena are apparent to the subject or their bed partner.

Sleep is a physiologically unique state in which movement disorders behave differently than in wake. Therefore, it might be interesting to perform fMRI in sleep (ideally both during REM and non-REM phases), as this might shed light on the unique fact that PD tends to be "silent" when the brain is asleep. Such data also may suggest how REM-related movement is giving us a clue to the earliest stages of basal ganglia dysfunction.

As this study suggests, the connection between RBD and PD is deserving of further investigation. If RBD is a reliable precursor of PD, lengthier longitudinal studies would be possible and, more importantly, neuroprotective disease-modifying therapies could be developed. ■

ABSTRACT & COMMENTARY

Distinct EEG Features May Help Prognostication of Patients with Early PAMM

By Peter B. Forgacs, MD

Instructor in Neuroscience and Neurology, Feil Family Brain and Mind Research Institute and Department of Neurology, Weill Cornell Medical College; Instructor in Clinical Investigation, The Rockefeller University, New York

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

SYNOPSIS: Early post-anoxic multifocal myoclonus (PAMM) traditionally has been considered a grave prognostic feature in patients who remain comatose after cardiac arrest. This study defines distinct electrographic phenotypes in the setting of PAMM with substantially different prognostic outcomes.

SOURCE: Elmer J, Rittenberger JC, Faro J, et al; Pittsburgh Post-Cardiac Arrest Service. Clinically distinct electroencephalographic phenotypes of early myoclonus after cardiac arrest. *Ann Neurol* 2016; Jun 28. doi: 10.1002/ana.24697. [Epub ahead of print].

Prognostication in patients who remain comatose after a cardiac arrest remains challenging. Clinical decision-making often is strained by the uncertainties of long-term outcomes, even after careful consideration of all clinical information and test results. Traditionally, early appearance (< 24 hours after the cardiac arrest) of myoclonic motor activity, so-called early post-anoxic multifocal myoclonus (PAMM), was considered to be a sign of severe, irreversible injury to widespread cortical areas, and thus, incompatible with full clinical recovery. More recently, an increasing number of patients have been reported to survive and functionally recover, even in the setting of early PAMM. However, it remains uncertain if these cases emerged as a consequence of improvements in post-arrest management or if they represent a distinct clinical subtype of PAMM. Elmer et al aimed to carefully characterize electrographic phenotypes of patients with PAMM and report outcomes for the defined subgroups respectively.

This study involved 69 patients with early PAMM from a cohort of 401 consecutive patients admitted to a single center after cardiac arrest for over a three-year period. The authors classified continuous EEG recordings of patients with early PAMM into four distinct patterns: 1) burst-suppression background with epileptiform discharges time-locked with the myoclonic jerks, 2) a more continuous background with discharges present that are also time-locked with the myoclonic jerks, 3) "subcortical" myoclonus with no epileptiform discharges present, and 4) "other" patterns that did not fit in the previous categories. The majority (74%) of patients with PAMM had EEGs consistent with pattern 1, while 12% of patients had pattern 2, 3% had subcortical myoclonic (pattern 3), and 11% belonged to the "other" category. The most important finding of the study is that none of the patients with pattern 1, 3, or 4 survived with favorable outcome; however, in striking contrast, four out of the eight (50%) patients with pattern 2 survived, and all four patients had favorable clinical outcomes (defined as discharge to home or acute rehabilitation). Importantly, in these cases, favorable recovery occurred even after the patients remained comatose one to two weeks after cardiac arrest.

The authors argued that these strikingly different prognostic outcomes can be explained by the different injury patterns related to the degree and extent of anoxic neuronal injury. They propose that pattern 1 could be considered a sub-type of burst-suppression pattern with identical bursts, which has been reported to be associated with universally poor outcome. These morphologically uniform bursts are speculated to be the consequence of widespread cortical damage resulting in loss of functional cortical networks and disinhibition of thalamic or brainstem "pacemakers." By contrast, the authors proposed that pattern 2 may represent a precursor of Lance-Adams syndrome. This syndrome is thought to be a result of selective loss of cerebellar Purkinje cells with preservation of cortical neurons in the setting of intermediate levels of hypoxia. The loss of Purkinje cells results in disinhibition of the reticular formation and, subsequently, synchronous activity of thalamic generators. This argument is supported by relative higher sensitivity of Purkinje cells to hypoxia compared to other neuronal sub-types and preservation of continuous EEG background in these patients indicating sparing of functional cortical networks. The authors speculated that preservation of consciousness and cognition — which is a hallmark of Lance-Adams syndrome — is suppressed by concomitant use of sedatives and multiple antiepileptic medications in these patients in the early phases of recovery after cardiac arrest.

■ COMMENTARY

This study confirms that early PAMM is a poor prognostic sign after cardiac arrest in the majority of patients with a notable exception: A small number of patients with continuous background activity on EEG, even in the setting of epileptiform discharges time-locked with myoclonic jerks, had significantly greater chances for recovery compared to patients with burst-suppression or other EEG patterns.

Several study limitations are worth mentioning. First, the authors did not report important clinical information that is part of routine post-cardiac arrest protocols in many centers — i.e., results of somatosensory-evoked potentials, neuron-specific enolase, neurological exam (i.e., motor or brainstem findings), circumstances of resuscitation (i.e., time to return of spontaneous circulation), or imaging findings, all of which may indicate the extent of anoxic damage and possibly support their speculations about mechanisms of the observed EEG patterns and their relation to outcomes. Furthermore, in the absence of other signs indicating overwhelming neuronal injury, burst-suppressed EEG by itself may not indicate irreversible loss of functional cortical networks. It has been suggested that some burst-suppressed patterns may even represent an energy-saving mode of thalamocortical circuitry to optimize metabolic functions. Lastly, the use of sedatives and hypothermia often used in this setting may contribute to development of suppressed background, also emphasizing a cautious approach based on this EEG pattern alone. Most importantly, however, the major study limitation is the inherent bias introduced by current clinical practices of withdrawal-of-care decisions that may have significantly affected the outcomes. It cannot be ruled out that clinicians were influenced by the EEG findings and that there may have been some patients who would have survived even with favorable outcome with EEG phenotypes other than in pattern 2. As the authors also noted, unless the study is replicated in a health system in which withdrawal-of-care is not routinely performed, the results of this study should not be readily translated to clinical practice to justify early withdrawal of therapy based on EEG morphology only. ■

Neurology [ALERT]

Stroke Alert

By Matthew E. Fink, MD

Community Education Improves Stroke Awareness and Appropriate Emergency Response

SOURCE: Skolarus LE, Zimmerman MA, Bailey S, et al. Stroke ready intervention: Community engagement to decrease prehospital delay. *J Am Heart Assoc* 2016;5:e003331 doi: 10.1161/JAHA.116.003331.

Acute stroke treatments have altered the prognosis of acute ischemic stroke dramatically, if administered within an appropriate time window. However, these treatments are seriously underused because of delay in hospital presentation. These delays are evident particularly in minority populations, especially in the African-American community. The authors initiated a community education program, aimed at altering health behaviors to increase stroke preparedness among African-American youth and adults in Flint, MI. Subjects observed one-minute video vignettes that taught symptom recognition and then were instructed to make 911 calls when vignettes indicated an acute stroke. Non-stroke vignettes recommended non-urgent and non-emergency responses to the participants. One hundred one participants completed the baseline assessments, and 68 completed a delayed post-test. Compared to baseline, an appropriate response to suspected stroke was improved in the post-testing group, indicating improved stroke recognition and appropriate emergency response. Community education programs are essential in our efforts to improve our overall success in treating acute ischemic stroke. ■

Triage to a Certified Stroke Center Reduces Early Mortality

SOURCE: Bekelis K, Marth NJ, Wong K, et al. Primary Stroke Center hospitalization for elderly patients with stroke. Implications for case fatality and travel times. *JAMA Intern Med* doi:10.1001/jamainternalmed.2016.3919.

In a national attempt to improve stroke care, there has been widespread certification of primary stroke centers (PSCs) by The Joint Commission. It has been assumed that outcomes will be better in the PSCs, but there have always been questions regarding how much additional time is acceptable to travel to a PSC, compared to a local hospital, in terms of successful treatment and outcomes. The investigators queried a Medicare database, examining the association of case fatality for patients with stroke when receiving care in a PSC vs. other hospitals, to identify the effects of prolonged travel time. This was a retrospective study of 865,184 elderly patients with stroke, with a mean age of 78.9 years, and 55.5% were female. The investigators found that 53.9% of the patients were treated in PSCs. In addition, they found that admission to a PSC was associated with a 1.8% lower seven-day mortality and a 1.8% lower 30-day case fatality. Fifty-six patients with stroke needed to be treated in a PSC to save one life at 30 days. In an analysis of the effect of additional travel time, receiving treatment in a PSC was associated with a survival benefit for patients who traveled less than 90 minutes. Traveling more than 90 minutes to reach a PSC offset any benefit of the PSC care. ■

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CME QUESTIONS

1. **Which of the following is true regarding impulse control disorders (ICDs) in Parkinson's disease (PD)?**
   a. ICDs are 3.5 times more likely to occur in those taking levodopa than those taking dopamine agonists.
   b. Individuals with PD have an extremely low risk (0.5%) of developing ICDs.
   c. ICDs occur only in association with oral dopamine agonists (pramipexole and ropinirole).
   d. Use of the transdermal patch rotigotine has been associated with lower risk of ICDs in PD.

2. **Peripheral neuropathy in multiple myeloma is:**
   a. never small fiber in nature.
   b. always related to POEMS (polyneuropathy, organomegaly, endocrinopathy, monoclonal component, and skin changes).
   c. found in < 10% of patients at time of diagnosis of myeloma.
   d. not made worse or better following chemotherapy.
   e. pathognomonic of a diagnosis other than myeloma.

3. **Which of the following statements about the association of traumatic brain injury (TBI) with late-life neurodegenerative diseases is most true?**
   a. TBI is not associated with late-life neurodegenerative diseases.
   b. TBI with loss of consciousness is associated with risk for Lewy body accumulation, progression of Parkinsonism, and Parkinson's disease, but not dementia, Alzheimer's disease, neuritic plaques, or neurofibrillary tangles.
   c. TBI is associated with late-life Alzheimer's disease.
   d. TBI with loss of consciousness has no neurological sequelae.

4. **Which of the following disorders of sleep may be prodromal precursors of Parkinson's disease?**
   a. Narcolepsy
   b. Obstructive sleep apnea
   c. Rapid eye movement behavior disorder
   d. Insomnia

5. **Following cardiac arrest and resuscitation, which of the following features is *not* a poor prognostic sign for neurological recovery?**
   a. Prolonged time of CPR before return of spontaneous circulation
   b. Multifocal myoclonus with burst-suppression pattern on EEG
   c. Widespread cortical ischemic injury on brain MRI
   d. Multifocal myoclonus with continuous background activity on EEG
   e. Prolonged coma with absent brain stem reflexes

6. **Education of the general community about the symptoms and signs of stroke improves the speed of emergency 911 calls.**
   a. True
   b. False

7. **Transport to a primary stroke center results in lower stroke mortality compared to treatment in other hospitals.**
   a. True
   b. False

[IN FUTURE ISSUES]

Update on Alzheimer's Disease Clinical Trials