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Neurology [ALERT®]

Evidence-based summaries of the latest clinical neurology research

ABSTRACT & COMMENTARY

Cognitive Outcomes After Mild Traumatic Brain Injury

By Nitin K. Sethi, MD

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SYNOPSIS: Mild traumatic brain injuries (mTBIs) may lead to adverse cognitive and neuropsychiatric outcomes. The pathways that lead to adverse cognitive outcomes remain to be scientifically elucidated. A prospective cohort study of 656 participants enrolled in the Transforming Research and Clinical Knowledge in TBI (TRACK-TBI) study found that at one year, 13.5% of participants with mTBI had poor cognitive outcome compared to 4.5% of controls, highlighting the need for better understanding of the mechanisms leading to poor cognitive and functional outcomes after mTBIs and interventions to optimize cognitive recovery.

SOURCE: Schneider ALC, Huie JR, Boscardin WJ, et al. Cognitive outcome 1 year after mild traumatic brain injury: Results from the TRACK-TBI study. *Neurology* 2022;98:e1248-e1261.

The authors in this prospective cohort study compared 656 participants 17 years of age or older (mean age 40.2 years, 36.6% female, 76.6% white) presenting to Level I trauma centers within 24 hours of mild traumatic brain injury (mTBI, defined as Glasgow Coma Scale score 13-15) with 156 demographically similar healthy controls enrolled in the Transforming Research and Clinical Knowledge in TBI (TRACK-TBI) study. All participants then were examined at two weeks, six months, and one year post-trauma and underwent a neuropsychological test battery of cognitive functions. This test battery consisted of five scores, capturing different aspects of cognitive function using three different tests. The Auditory Verbal Learning test looked at immediate and delayed recall, the Trail Making Tests A and B were administered for assessment of executive functioning, and the Processing Speed Index from the Wechsler Adult Intelligence scale also was administered.

A definition of cognitive impairment was determined by using demographically adjusted cutoffs. The investigators determined that the

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ninth percentile threshold would be the cutoff for cognitive impairment, consistent with other studies that were completed under the TRACK-TBI research program.

Poor one-year cognitive outcome was defined as cognitive impairment below the ninth percentile of normative data on two or more cognitive tests. Cognitive decline was defined as a change in score (one-year score minus best two-week or six-month score) exceeding the 90% reliable change index on two or more cognitive tests. Associations of poor one-year cognitive outcome with one-year neurobehavioral outcomes also were performed.

After comparison of baseline characteristics, logistic regression was used to build a prediction model. The cohort of mTBI participants with poor one-year cognitive outcome had worse one-year functional outcome, more neurobehavioral symptoms, greater psychological distress, and lower satisfaction with life.

At one-year follow-up, 13.5% of participants with mTBI had a poor cognitive outcome vs. 4.5% of control subjects (P = 0.003). Non-white race, lower education, lower income, lack of health insurance, hyperglycemia, preinjury depression, and greater injury severity correlated with poor one-year cognitive outcome. The authors, in their prediction model, found that education, health insurance, preinjury depression, hyperglycemia, and Rotterdam computed tomography score of 3 or higher were independently associated with more than twofold increased odds of poor one-year cognitive outcome.

■ COMMENTARY

There is no standardized definition of mTBI.[1] In the absence of validated biofluid (blood/cerebrospinal fluid) and imaging biomarkers, separating concussion as a distinct pathophysiological entity from mTBI is not easy, leading to misconceptions and biases in the diagnostic process, uninterpretable science, poor clinical guidelines, and confused policy.

Currently mTBI is defined as a traumatically induced physiological disruption of brain function manifested by at least one of the following: any period of loss of consciousness, any retrograde or anterograde amnesia, any alteration in the level of consciousness, and focal neurological deficit(s) that may or may not be transient. Patients are classified as experiencing mTBI when loss of consciousness is approximately 30 minutes or less, they have an initial Glasgow Coma Scale (GCS) score of 13-15, and post-traumatic amnesia (PTA) does not exceed 24 hours.[2]

Historically, mTBI was used to describe patients briefly disabled following a head injury, with the assumption this was a transient disorder of brain function without long-term sequelae. Now it is well known that symptoms of mTBI are highly variable in duration and may persist for many years with no reliable early predictors of outcome.

In one study of 53 patients with mTBI, cognitive function was assessed at bedside within 24 hours post-injury. Compared to 28 healthy controls, mTBI patients exhibited significantly worse performance on Mini-Mental State Examination, Frontal Assessment Battery, naming, incidental memory, immediate memory, learning, and delayed recall. Patients with lower educational level had higher rates of cognitive impairment.

There was no difference in cognitive impairment between patients with or without loss of consciousness.[3] It is likely that a significant number of patients with mTBI experience cognitive deficits acutely after the head impact exposure. In some of these patients, these deficits lead to long-term adverse cognitive and neuropsychiatric outcomes and poor quality of life.

Studies addressing factors that lead to adverse cognitive, neuropsychiatric, and functional outcomes after mTBI are needed. Evidence-based recommended practices then can be implemented early in patients with mTBI to prevent these adverse outcomes. ■

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ABSTRACT & COMMENTARY

Does Amantadine Treatment Reduce Levodopa-Induced Dyskinesias?

By Andrea Lee, MD

Assistant Professor of Clinical Neurology and Assistant Attending Neurologist, New York-Presbyterian/Weill Cornell Medical College

SYNOPSIS: This retrospective cohort study compared the effect of amantadine on levodopa-induced dyskinesia (LID) onset with use of anticholinergics and monoamine oxidase type B inhibitors in patients with Parkinson's disease. The authors concluded that early treatment with amantadine may delay LID onset more than treatment with other symptomatic agents.

SOURCE: Wang CC, Wu TL, Lin FJ, et al. Amantadine treatment and delayed onset of levodopa-induced dyskinesia in patients with early Parkinson's disease. *Eur J Neurol* 2022;29:1044-1055.

To improve motor symptoms in people with Parkinson's disease (PD), levodopa is a mainstay of treatment. However, levodopa-induced dyskinesia (LID), which can severely impair the patient's quality of life, is a risk of long-term exposure to levodopa. Amantadine currently is the only N-methyl-D-aspartate (NMDA) receptor antagonist that provides symptomatic relief for patients with dyskinesia; it often is used in combination with levodopa for patients with LID. Amantadine also may be used as a symptomatic treatment for early PD. Clinical observations suggest that, compared to those who receive other symptomatic treatments, patients who receive amantadine seem to have a delayed onset of LID. Evidence suggests that amantadine likely is effective and useful for the early treatment of PD, but little real-world evidence exists regarding the use of amantadine for lowering the risk of LID.

This hospital-based retrospective cohort study used electronic medical records from Jan. 1, 2009, to Oct. 31, 2016, to compare the time of LID onset in patients treated with amantadine, anticholinergics, or monoamine oxidase type B inhibitors. The analyses included 807, 661, and 518 patients at six-, 12-, and 18-month landmark points, respectively. Among the patients included in the six-month landmark analysis, the two groups were comparable in terms of sex distribution and parkinsonism symptom duration. Overall, the mean duration of symptoms was less than two years, and the mean Hoehn and Yahr stage was approximately 1.6, which was concordant with the definition of early PD. LID was defined as the occurrence of peak-dose dyskinesia, diphasic dyskinesia, and off-dystonia. The clinical manifestations of LID were documented in the medical records by experienced movement disorder specialists and reviewed by two investigators.

Amantadine use was associated with delayed LID onset in the six- and 12-month landmark analyses, with adjusted hazard ratios of 0.65 (95% confidence interval [CI] = 0.49 to 0.86) and 0.64 (95% CI = 0.47 to 0.88), respectively, but not in the 18-month landmark analysis.

■ COMMENTARY

This study investigated the association between early amantadine treatment and LID onset in patients with PD. The results demonstrated that patients with early PD who received amantadine treatment for at least six months had a significantly lower risk of developing LID than those who received either anticholinergics or MAOBIs for at least six months, but the result was not statistically significant in the 18-month landmark analysis.

The authors postulated that the reasons for the potential beneficial effects of early amantadine treatment on the occurrence of LID may not have resulted from its anti-dyskinetic mechanism only; rather they related amantadine's protective properties against LID development to those observed in PD models in the laboratory, including anti-glutamate activity, reduction in release of

proinflammatory factors from activated microglia, and induction of glial-derived neurotrophic factor expression in astroglia. Since chronic astroglia and microglia activation are associated with neuroinflammation, thereby affecting synaptic activity and neuroplasticity leading to LID, the authors postulated that the anti-inflammatory activity of amantadine could theoretically attenuate this inflammatory process.

Possible explanations for the nonsignificant finding in the 18-month landmark analysis is the exclusion of patients with dyskinesia during the landmark periods; hence the nonsignificant finding could have resulted from the low number of patients analyzed at the 18-month landmark point, leading to a loss of power.

There is a possibility patients who were analyzed at 18 months were more clinically stable or responded better to the treatment than those analyzed at six and 12 months. Therefore, a lower risk of dyskinesia was found in the former group of patients. Overall, this study suggests that amantadine, an NMDA receptor antagonist, not only provides symptomatic relief for patients with LID, but may also delay the onset of LID in early PD patients. ■

ABSTRACT & COMMENTARY

Outcomes of Progressive Multifocal Leukoencephalopathy Treated with IL-7

By Hai H. Hoang, MD

Assistant Professor of Clinical Neurology, Weill Cornell Medical College

SYNOPSIS: Progressive multifocal leukoencephalopathy (PML) is a severe demyelinating disease of the central nervous system caused by the reactivation of the JC virus. The authors of this study conducted a multi-centered retrospective observational study on 64 patients with PML who were treated with recombinant human IL-7 (RhIL-7). Overall, the one-year all-cause survival following start of RhIL-7 was 55% and similar among human immunodeficiency virus/acquired immunodeficiency syndrome, hematological malignancies, and primary immunodeficiencies.

SOURCE: Lajaunie R, Mainardi I, Gasnault J, et al. Outcome of progressive multifocal leukoencephalopathy treated by interleukin-7. *Ann Neurol* 2022;91:496-505.

Progressive multifocal leukoencephalopathy (PML) is a severe demyelinating disease of the central nervous system (CNS) caused by the reactivation of the JC virus (JCV) in hosts with impaired cellular immunity (innate immune system). Since there is no antiviral drug known to be active against JCV, recovery of the immune system's antiviral response remains, to date, the only alternative to control PML.

Emerging evidence suggests PML remission can be achieved with novel immunotherapeutic approaches that promote the recovery anti-JCV immune responses, including immune checkpoint blockade, adoptive transfer of anti-polyomavirus specific T cells, and use of filgrastim or cytokines, including interleukin-7 (IL-7). IL-7 is a cytokine that is pivotal in regulating peripheral naïve T cell survival and homeostasis. Recombinant human IL-7 (RhIL-7) is a glycosylated protein synthesized by genetically engineered cell lines.

Lajaunie et al performed a retrospective multicenter study aimed at looking at the 12-month survival rates of patients with PML after RhIL-7 initiation. The study evaluated patients from 2007-2020 at multiple hospitals in France. Sixty-four of the 85 eligible patients receiving RhIL-7 were included in the study. Underlying diseases in the patients were 42% with human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS), 25% with hematological malignancies, 20% with primary immunodeficiencies, 6% with solid organ transplantation, and 6% with chronic inflammatory diseases.

There were no significant differences in the cerebrospinal fluid (CSF) JCV polymerase chain reaction load among the groups. Administration of RhIL-7 was at a dosage of 10 µg/kg/injection in 86% of patients and 20 µg/kg/injection in 14% of patients, and most patients (88%) received three or more injections. All patients with HIV/AIDS received optimized combined anti-retroviral therapy following PML diagnosis with control of HIV-1 replications in all except one patient.

One-year survival following the start of RhIL-7 was 55% and was similar among patients with HIV/AIDS, hematological malignancies, and

primary immunodeficiencies. Survival was associated with > 50% increase in blood lymphocytes and a statistically significant reduction in JCV deoxyribonucleic acid in patients' CSF during the first month of treatment with IL-7. Thirty percent of treated patients reported side effects, mostly consisting of local injection reactions and flu-like symptoms (40%). PML immune reconstitution inflammatory syndrome was diagnosed in 8% and was associated with clinical worsening with median increase in Modified Rankin Scale score of 1.

■ COMMENTARY

The authors concluded that the administration of RhIL-7 in patients with PML seems to have a beneficial effect in patients with hematological malignancies, primary immune deficits, and transplant recipients. Quantitatively, CD4 T cell count increased and CSF JCV replication decreased during the treatment, but it was not possible to ascertain whether they depended on RhIL-7 therapy, immune restoration through combined anti-retroviral therapy, withdrawal of immunosuppressive drugs, or a combination.

Limitations of this study include its observational, retrospective, and non-comparative design and inability to control for confounding variables, such as additional treatments with the RhIL-7 medication. Overall, this study presents a promising therapy for a neurologic disease with very few treatment options. Future studies should focus on a prospective study with an age- and sex-matched control to truly determine the efficacy of RhIL-7. ■

ABSTRACT & COMMENTARY

Antibody Profile in Refractory Myasthenia Gravis

By Michael Rubin, MD

Professor of Clinical Neurology, Weill Cornell Medical College

SYNOPSIS: In retrospective studies of patients with generalized myasthenia gravis, those who are refractory to multiple treatments have disease onset at an earlier age, are more likely to have thymic pathology, and are more likely to be double-seronegative (neither acetylcholine receptor nor muscle-specific receptor tyrosine kinase antibodies).

SOURCE: Veltsista D, Kefalopoulou Z, Tzartos J, Chroni E. Autoantibody profile in myasthenia gravis patients with a refractory phase. *Muscle Nerve* 2022; Feb 23. doi: 10.1002/mus.27521. [Online ahead of print].

Drug-refractory myasthenia gravis (MG), seen in 10% to 15% of patients, is defined as disease that is clinically unchanged or worse despite corticosteroid treatment and at least two additional immunosuppressive agents, used in adequate doses for an adequate time. It has been associated with female sex, younger age at onset, thymoma, and anti-muscle-specific receptor tyrosine kinase (MuSK) antibodies, and it presents more frequently with generalized disease, bulbar symptoms, and life-threatening events. Is there an antibody profile associated with refractory MG?

In this retrospective study, MG patients, followed for at least 18 months and clinically stable for three months, at the Neuromuscular Center, Department of Neurology, University Hospital of Patras, Rion, Greece, were included. Diagnosis was based on a history of fluctuating weakness and fatigue, exclusion of alternative diagnoses, and the presence of either antibodies against the nicotinic acetylcholine receptor (AChR) or MuSK, abnormal repetitive nerve stimulation (RNS) studies, or abnormal single-fiber electromyography (SF-EMG). Disease extent and severity were measured using a) the Myasthenia Gravis Foundation of America (MGFA) classification, I-V classes, and b) the quantitative myasthenia gravis (QMG) score (range, 0-39).

Refractory disease was defined as being either a) MGFA class III for at least 12 months, b) less than MGFA class III, with at least two relapses requiring intravenous immunoglobulin (IVIG) or plasmapheresis (PLEX), despite steroid and other immunosuppressant treatment in adequate dosage for at least 12 months, or c) less than MGFA class III, requiring prolonged, high-dose, potentially harmful immunosuppressive therapy. Statistical analysis comprised the Mann-Whitney U test and the Wilcox signed-rank test, with significance set at $P < 0.05$.

Among 113 MG patients analyzed, 15 (13.3%) were refractory, and, compared to the non-refractory patients, were younger and with an

earlier age of onset, more often had thymic pathology, and more often had undergone thymectomy, but they did not differ with respect to MGFA class at diagnosis, disease duration, or time to treatment initiation. Refractory MG patients had neither MuSK nor low-density lipoprotein receptor-related protein 4 (LRP4) antibodies, and they were more likely to be double-seronegative (neither AChR nor MuSK antibodies) than the non-refractory group. Both seropositive and seronegative refractory MG patients were comparable with regard to age at diagnosis, time interval to refractory phase, refractory treatment, and thymectomy status. Refractory, double-seronegative MG patients may represent a distinct class of MG requiring individualized, targeted treatment.

■ COMMENTARY

Among 990 patients with MG from 15 hospitals across Spain, reviewed in an observational, cross-sectional, multicenter study based on the Spanish MG registry, 84 (8.5%) were refractory. Of these refractory patients, 68 demonstrated anti-AChR antibodies, five were positive for anti-MuSK antibodies, 10 were seronegative, and one was double-seropositive (anti-AChR and anti-MuSK antibodies). Female sex (75% were women), younger age at onset (mean age of onset, 44.4 years), and MuSK positivity (6%) were found to be significantly related to having refractory MG, as was presenting as generalized disease (77.5% at onset, 92.3% ultimately), with bulbar symptoms (47.5%), and with life-threatening events (13.8%). Among seropositive patients, rituximab and tacrolimus were the drugs that refractory patients responded to the most, but among drug-refractory seronegative patients, 80% did not respond to any drug. Over a follow-up period of 9.8 years, 100% of anti-MuSK-positive patients and 42.6% of anti-AChR-positive patients achieved remission, compared to 10% of seronegative patients, underscoring the need for new drugs to treat this group of MG patients.[1] ■

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1. Cortes-Vicente E, Alvarez-Velasco R, Pla-Junca F, et al. Drug-refractory myasthenia gravis: Clinical characteristics, treatments, and outcome. *Ann Clin Transl Neurol* 2022;9:122-131.

ABSTRACT & COMMENTARY

Neurodegeneration Biomarkers in Patients with Subjective Cognitive Complaints

By Makoto Ishii, MD, PhD

Assistant Professor of Neuroscience and Neurology, Feil Family Brain and Mind Research Institute, Department of Neurology, Weill Cornell Medical College

SYNOPSIS: In individuals with subjective cognitive decline, multiple biomarkers of neurodegeneration were found to add predictive values beyond amyloid and tau biomarkers; however, the various neurodegeneration biomarkers were not equivalent and should not be used interchangeably.

SOURCE: Ebenau JL, Pelkmans W, Verberk IMW, et al. Association of CSF, plasma, and imaging markers of neurodegeneration with clinical progression in people with subjective cognitive decline. *Neurology* 2022;98:e1315-e1326.

Abnormal amyloid-beta aggregation, neurofibrillary tau tangles, and neurodegeneration are the classic hallmarks of Alzheimer's disease (AD), and, until recently, these pathological changes could be identified only in postmortem brains. With the development of fluid and imaging biomarkers, these pathological changes now can be identified in vivo in individuals, even prior to cognitive symptoms. This has led to the establishment of the ATN classification (A: amyloid-beta; T: tau; N: neurodegeneration), where amyloid-beta pathology can be measured by cerebrospinal fluid (CSF) amyloid-beta or amyloid positron emission tomography (PET) and tau pathology by CSF phosphorylated tau or tau PET. Although amyloid-beta and tau biomarkers are rapidly becoming established, there are a variety of proposed biomarkers of neurodegeneration, including atrophy on magnetic resonance imaging (MRI), hypometabolism on fluorodeoxyglucose (FDG) PET, CSF total tau, and blood-based biomarkers, such as neurofilament light (NfL) and glial fibrillary acidic protein (GFAP). Since the neurodegeneration biomarkers used in the ATN classification vary considerably and may reflect different aspects of neurodegeneration, it is not clear if the different neurodegeneration biomarkers are equivalent and, therefore, interchangeable. Importantly, whether neurodegeneration markers have predictive value for clinical progression

beyond amyloid-beta and tau biomarkers has not been established.

Ebenau and colleagues sought to address these gaps in our knowledge by evaluating neurodegeneration biomarkers in a longitudinal study of 401 individuals with subjective cognitive decline from the Alzheimer Center Amsterdam. Structural MRI 3D T1-weighted images, non-fasting blood samples, and lumbar puncture for CSF analysis were obtained. Mini-Mental State Examination (MMSE) was assessed annually and served as the longitudinal measure of global cognition. The following neurodegeneration biomarkers were examined: CSF total tau, medial temporal atrophy visual rating on MRI, hippocampal volume on MRI, serum NfL, and serum GFAP.

The authors found that the various neurodegeneration biomarkers were modestly to moderately correlated (range, -0.28 to 0.58). Serum NfL and GFAP were strongly correlated (range, 0.58; $P < 0.01$), while CSF phosphorylated tau and total tau were very strongly correlated (range 0.89; $P < 0.001$). Adjusting for age and sex resulted in a drastic reduction in the coefficients, but the correlation between CSF phosphorylated tau and total tau remained very strong. Using uncorrected models, all neurodegeneration biomarkers predicted clinical progression to mild cognitive impairment (MCI) or dementia. Adding covariates of age, sex, CSF amyloid-beta, and CSF phosphorylated tau to the model attenuated all hazard ratios (HR).

However, hippocampal volume, serum NfL, and serum GFAP added significant predictive value beyond the amyloid-beta and phosphorylated-tau biomarkers (HR, 1.52 [95% confidence interval (CI), 1.11 to 2.09]; HR, 1.51 [95% CI, 1.05 to 2.17]; HR, 1.50 [95% CI, 1.04 to 2.15], respectively). CSF total tau was excluded from the final analysis because of its collinearity with CSF phosphorylated tau. Finally, although CSF total tau, hippocampal volume, and serum GFAP all predicted MMSE slope or cognitive decline over time, only hippocampal volume added predictive value beyond amyloid-beta and phosphorylated tau biomarkers.

■ COMMENTARY

Although the recent advances in biomarkers to classify AD and predict clinical progression in individuals with no or minimal clinical symptoms have been truly remarkable, there is room for improvement. In this present study, the authors found that using neurodegeneration biomarkers of hippocampal volume, serum NfL, or serum GFAP improved prediction of clinical progression beyond simply using amyloid-beta and phosphorylated tau biomarkers. An important finding was that not all neurodegeneration biomarkers added predictive value. Medial temporal visual rating scores were found to be too crude a measure to accurately predict decline in cognitively normal individuals. Moreover, CSF total tau commonly is used as a neurodegeneration biomarker, but CSF total tau may not be an appropriate independent biomarker of neurodegeneration since it strongly correlated with CSF phosphorylated tau.

A major strength of this study is the use of multiple neurodegeneration biomarkers from different modalities in a relatively large study population. However, there are notable limitations. As noted by the study authors, the list of neurodegeneration markers examined was not exhaustive and notably did not include FDG-PET or other MRI atrophy measures. Furthermore, the study population consisted of individuals with subjective cognitive decline presenting at a memory clinic. This may limit the ability to generalize the findings to other populations. Also, many of the biomarkers used do not have optimal cutoff values, which may result in different results, depending on which cutoff values are used. Until a validated cutoff for the biomarkers is established, this may limit the general use of these biomarkers on an individual level.

Finally, a low percentage of individuals (16%) had clinical progression to MCI or dementia during this study. This was attributed by the authors to the relatively short follow-up duration of 3.8 years and the overall younger age (mean 60.9 years). Future studies with longer follow-up duration and older study population will be needed to verify and validate the findings from this study.

Despite any limitations, this study eloquently highlights the importance of selecting appropriate neurodegeneration biomarkers when using the ATN framework and that the different neurodegeneration biomarkers should not be treated as equivalent. Unfortunately, this study could not find a single "most suitable" biomarker for neurodegeneration, which would be useful when bringing these biomarkers to more general clinical practice. Finally, identifying additional biomarkers beyond the ATN framework, including vascular, inflammatory, and metabolic biomarkers, should remain a research priority, since these other classes of biomarkers could add additional diagnostic and predictive value beyond ATN. ■

CME OBJECTIVES

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

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

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CME QUESTIONS

1. **Which of the following statements regarding cognitive outcome after mild traumatic brain injury (mTBI) is true?**
   a. An mTBI does not lead to long-term adverse cognitive outcome.
   b. Few patients with mTBI experience cognitive deficits acutely after the head impact exposure.
   c. Some patients with mTBI and acute cognitive deficits also have long-term adverse cognitive and neuropsychiatric outcomes and poor quality of life.
   d. All patients with mTBI experience cognitive deficits acutely.
2. **Levodopa-induced dyskinesias may be attenuated by which of the following treatment strategies?**
   a. Addition of catechol-O-methyltransferase medication to levodopa therapy
   b. Changing from immediate-release levodopa to extended-release levodopa
   c. Adding amantadine to levodopa regimen
   d. Adding pramipexole or ropinirole to levodopa therapy
3. **Which of the following treatment strategies is *not* considered in the treatment of progressive multifocal leukoencephalopathy?**
   a. Recombinant human interleukin-7
   b. Steroids
   c. Withdrawal of immunosuppressants
   d. Initiation of combined anti-retroviral therapy
4. **Which of the following statements regarding refractory myasthenia gravis patients is *false*?**
   a. They are more likely to have low-density lipoprotein receptor-related protein 4 antibodies.
   b. They are more likely to have an older age of onset, in the sixth decade and beyond.
   c. They are more likely to be male.
   d. They are more likely to be double seronegative (neither acetylcholine receptor nor muscle-specific receptor tyrosine kinase antibodies).
5. **When investigating the association of neurodegeneration biomarkers with clinical progression in people with subjective cognitive decline, which of the following neurodegeneration biomarkers did *not* predict clinical progression beyond amyloid and tau biomarkers?**
   a. Medial temporal atrophy visual rating on magnetic resonance imaging (MRI)
   b. Hippocampal volume on MRI
   c. Serum neurofibrillary light chain
   d. Serum glial fibrillary acidic protein