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Neurology [ALERT®]

Evidence-based summaries of the latest clinical neurology research

ABSTRACT & COMMENTARY

DaTSCAN to Distinguish Parkinson's Disease from Secondary Parkinsonism

By Claire Henchcliffe, MD

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Dr. Henchcliffe reports she is on the speakers bureau and advisory board for GE, Teva Pharmaceutical Industries, and UCB; advisory board for Allergan and USWorldmeds; receives grant/research support from Biogen and Kaneka; and does CME program development and presentation for MedIQ.

SYNOPSIS: A meta-analysis of five studies determined 86% sensitivity and 83% specificity in distinguishing Parkinson's disease from vascular parkinsonism, and 86% sensitivity and 98% specificity in distinguishing Parkinson's disease from drug-induced parkinsonism using DaTSCAN imaging.

SOURCE: Brigo F, et al. [^{123}I]FP-CIT SPECT (DaTSCAN) may be a useful tool to differentiate between Parkinson's disease and vascular or drug-induced parkinsonisms: A meta-analysis. *Eur J Neurol* 2014;21:1369-1376.

DaTSCAN imaging makes use of the dopamine transporter (DAT) ligand [^{123}I]FP-CIT used with SPECT to provide a means to visualize the integrity of the nigrostriatal dopaminergic system. DaTSCAN has been approved in the United States to aid in evaluation of patients in whom Parkinson's disease (PD) and certain other related neurodegenerative disorders are suspected. Brigo and colleagues now report results of a meta-analysis aiming to evaluate the usefulness of DaTSCAN in distinguishing PD, in which an abnormal scan is expected, from vascular parkinsonism (VP) and drug-induced parkinsonism (DIP), in which normal scans are expected. The meta-analysis included prospective and retrospective studies that examined DaTSCAN in cases of unclear clinical parkinsonism, in which final diagnoses included PD, VP, and/or DIP. Case-control studies were excluded. Five studies published between 2001 and 2013 met criteria for inclusion in the statistical analysis out of an initial 31 studies provisionally identified. Comparing DaTSCAN with final diagnosis, polled measures for PD vs VP yielded a sensitivity of 86.2% (95% confidence interval

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[CI], 81.3-90.1) and specificity of 82.9% (95% CI, 67.9-92.8%) along with a positive likelihood ratio (PLR) of 4.813 (95% CI, 1.523-15.211) and negative likelihood ratio (NLR) of 0.190 (95% CI, 0.139-0.259). Ability of DaTSCAN to diagnose PD vs DIP when compared with final diagnosis yielded a sensitivity of 86.2% (95% CI, 81.3-90.1) and specificity of 93.8% (95% CI, 69.8-99.8%), with a PLR of 5.366 (95% CI, 1.913-15.050) and NLR of 0.178 (95% CI, 0.125-0.253). There are certain limitations of the studies included. Two studies derived from a single group within a short time period, leading to the possibility that duplicate data were included. Moreover, diagnostic criteria were not reported for VP and DIP. Three studies did not report whether clinical diagnosis was made blinded to DaTSCAN results, and two studies did not report whether DaTSCAN results were interpreted while blinded to clinical diagnosis.

■ COMMENTARY

DaTSCAN was approved by the FDA in 2011 for use as an adjunct to clinical diagnosis in cases of parkinsonism with a suspicion for dopamine deficiency, such as PD, multiple system atrophy, or progressive supranuclear palsy. A recent study from Adler and colleagues highlighted diagnostic difficulty, and, using data from the Arizona Study of Aging and Neurodegenerative Disorders, they found that clinical diagnosis was only 88% sensitive and 68% specific for PD when compared to neuropathological diagnosis.[1] Moreover, since PD and many of its mimics have an insidious onset with clinical overlap, the risk of misdiagnosis is particularly high in early disease. This low diagnostic accuracy not only directly impacts patients and their families, but also "dilutes" PD cohorts enrolled in clinical studies. Thus, it is imperative that objective and accurate diagnostic biomarkers are developed. DaTSCAN and related neuroimaging modalities hold much hope in this regard.

As clinicians gain experience in how best to employ this test in practice, this meta-analysis by Brigo and colleagues is therefore a worthwhile addition to the literature. Most importantly, it finds that DaTSCAN is likely to be helpful in distinguishing cases of PD vs VP and DIP in which there may be clinical uncertainty. In both cases, this is predicted to alter clinical decision-making. For example, in the case of DIP, it opens a different diagnostic avenue to patients who otherwise would need to taper off antipsychotic medications for further clinical evaluation. However, as the authors note, their study highlights a number of limitations in the published literature so far. Many of the studies are small, and of the five studies included in this report, two had 15 or fewer participants. There are methodological variations in scanning that are difficult to fully account for. Clinical data reported varied between studies, and three of the studies included did not report participant age, gender, or disease duration. Finally, the use of DAT imaging is limited at this time in differentiating PD from Parkinson's plus disorders, such as multiple system atrophy or progressive supranuclear palsy, that account for many of the misdiagnosed cases seen in clinicopathologic studies. Therefore, this report should stimulate further investigations to support how best to use DaTSCAN in clinical practice. ■

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ABSTRACT & COMMENTARY

Hypoperfusion Response During Cortical Spreading Depolarizations

By Halinder S. Mangat, MD

Assistant Professor of Clinical Neurology, Weill Cornell Medical College

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

SYNOPSIS: Cortical spreading depolarizations (CSD) are common after severe brain trauma and are accompanied by alterations in cerebral blood flow physiology. In this study, the inverse neurovascular coupling

is described, demonstrating cerebral hypoperfusion in response to CSD. This may be a novel mechanism of secondary brain injury.

SOURCE: Hinzman JM, et al. Inverse neurovascular coupling to cortical spreading depolarizations in severe brain trauma. *Brain* 2014;137:2960-2972.

This study examines and describes the occurrence of an inverse neurovascular coupling response in peri-contusional brain tissue as a potential and novel mechanism for secondary brain injury.[1] Electrocorticography recordings were coupled with peri-contusional cerebral blood flow, recorded using a thermal diffusion probe and a brain oximetry probe. A total of 876 recordings of cortical spreading depolarizations (CSD) were made in 17 of 24 patients with traumatic brain injury, with 106 days of data recording. Cerebral blood flow (CBF) data were limited to 39% of the study duration due to technical reasons. Both physiological neurovascular coupling (hyperemia) as well as inverse coupling (hypoperfusion) were seen in 42% of patients, while no CBF changes were seen in the remaining patients.

There appeared to be a relationship between the vascular response to CSD and cerebral autoregulation. Patients with a hyperemic response had intact autoregulation, whereas those with hypoperfusion had impairment in autoregulation. In one patient with a transformation from a hyperemic to hypoperfusion response, autoregulation had worsened. Although baseline CBF was comparable in both response types, if initial CBF was in the ischemic range, the majority of responses resulted in hypoperfusion, and CSD duration was longer in these episodes. Although patients with increased ischemic duration had worse outcomes, there was no difference in outcomes based on those with and without CSDs.

■ COMMENTARY

CSDs have been described following several acute neurological injuries and are associated with poor outcome.[2-4] CSD is an electrophysiological phenomenon resulting in complete and sustained depolarization of neurons and astrocytes, and it causes complete loss of ionic cell membrane gradients.[5] CSD is accompanied by a vascular response, which may be of three possible types — none, transient hyperemia (physiological hyperdynamic response), or vasoconstriction causing hypoperfusion (inverse hemodynamic response).

Following CSD, energy-dependent ion pumps attempt to re-establish ionic gradients and cause depletion of metabolic substrates.[6,7] These substrates are supplied by hyperemia associated with CSD. However, if there is hypoperfusion during CSD, there is cellular hypoxia and reduction in metabolic substrate provision while demand is increased, resulting in further neuronal injury. The hyperemic response after CSD has been demonstrated in humans. This study confirms the presence of an inverse neurovascular response in humans after brain injury. A transformation of hemodynamic response from hyperemic to hypoperfusion is also demonstrated in two patients.

[The findings from this study on the occurrence of an inverse neurovascular coupling response in peri-contusional brain tissue may provide insight into novel mechanisms of secondary neuronal injury after brain trauma.]

In addition, the correlation with cerebral autoregulation has not been demonstrated previously. Whether the state of dynamic autoregulation entirely determines the type of hemodynamic response to CSD remains to be evaluated. These findings may provide insight into novel mechanisms of secondary neuronal injury after brain trauma. Poor autoregulation after severe traumatic brain injury is associated with worse outcome. It is likely that altered electrophysiological and hemodynamic responses are both a result of the primary injury and contribute to secondary injury and, therefore, are associated with neuronal injury and likely worse clinical outcomes. ■

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ABSTRACT & COMMENTARY

Utility of Anti-JC Virus Antibody Index to Assess the Risk of PML in Natalizumab-Treated MS Patients

By Jai S. Perumal, MD

Assistant Professor of Neurology, Weill Cornell Medical College

Dr. Perumal is on the speakers bureau for Biogen Idec, Teva Pharmaceuticals, Genzyme Corp., and Acorda Therapeutics.

SYNOPSIS: This study suggests that we may further define the risk of progressive multifocal leukoencephalopathy associated with natalizumab treatment based on individual anti-JC virus antibody index values rather than anti-JC virus antibody-positive or -negative status alone.

SOURCE: Plavina T, et al. Anti-JC virus antibody levels in serum or plasma further define risk of natalizumab-associated progressive multifocal leukoencephalopathy. *Ann Neurol* 2014; Oct 1. Doi: 10.1002/ana.24286.

Natalizumab is a monoclonal antibody that is FDA-approved for the treatment of relapsing-remitting multiple sclerosis (MS). Among the available options to treat MS, it is one of the most effective. The greatest concern with natalizumab treatment is the risk of developing progressive multifocal leukoencephalopathy (PML). The factors known to increase the risk of PML in natalizumab-treated patients include positive JC virus antibody status, longer duration of treatment, and prior immunosuppressive therapy use; the most significant among these is JC virus antibody status. Table 1, taken from the manufacturer prescribing information for natalizumab, provides estimated risk based on known risk factors.

When it was initially investigated, the results of the JC virus antibody test were reported simply as positive or negative, and risk assessments were based on positive or negative status alone, as noted in Table 1. More recently, risk has been quantified using an anti-JC virus index value, calculated from a two-step ELISA antibody assay of serum/plasma. An index of < 0.2 is designated as negative, > 0.4 positive, and a value > 0.2 but < 0.4 is designated as "indeterminate" and further evaluated by a confirmatory test.

The purpose of this study was to determine if the risk of PML associated with natalizumb can be further defined based on index values, and not merely by JC virus antibody, negative vs positive, status alone. A total of 2522 patients who were on natalizumab and who were JC virus antibody-positive and did not have PML, and 71 natalizumab-treated patients who were JC virus antibody-positive and who developed PML were included in the study. The subjects were either participants from the clinical trials of natalizumab or post-marketing use. For the analysis, subjects were divided into a test data set of 1039 non-PML and 45 PML patients and a validation set of 1488 non-PML and 26 PML patients. Integrated analysis of the combined data set of 2522 non-PML patients and 71 PML patients was also performed. In PML patients only, samples that were collected at least 6 months prior to the PML diagnosis were included.

The analysis showed that patients who developed PML had significantly higher JV antibody index than non-PML patients in the test data set (median = 2.4 vs 1.4, $P < 0.0001$) and the validation test set (median = 2.3 vs 1.9, $P = 0.0199$). Using predicted probabilities for JC virus antibody-positive patients with no prior immune suppression, with an antibody index of 0.9 to 1.5, the risk of PML was about 0.1 per 1000 from 25 to 48 months and 1.3 per 1000 from months 49 to 72. For JC

Table 1. Estimated U.S. Incidence of Progressive Multifocal Leukoencephalopathy Stratified by Risk Factor

Anti-JCV Antibody Negative	TYSABRI Exposure	Anti-JCV Antibody Positive	
		No Prior Immunosuppressant Use	Prior Immunosuppressant Use
< 1/1000	1-24 months	< 1/1000	1/1000
	25-48 months	3/1000	13/1000
	49-72 months	7/1000	9/1000

virus antibody-positive patients with no prior immune suppression who have a JC virus antibody index of > 1.5, the risk of PML was about 1 per 1000 from 25 to 48 months and ranged from 8.1 to 8.4 per 1000 from months 25 to 72. The association of higher index values with higher risk of PML was not significant for patients who were treated with prior immune suppression, and did not appear to help determine PML risk based on index values in this group. There was no association between the index value and duration on natalizumab treatment or prior immunosuppression. Long-term stability of the index values for an individual patient was assessed over a period of 18 months. Eighty-seven percent of those who were JC virus antibody-negative at baseline remained negative during the entire 18 months. Ninety-six percent to 97% (each data set respectively) of patients who were negative at baseline either remained negative, or if they converted, were below an index value of 1.5.

■ COMMENTARY

This study helps further define the risk of natalizumab-associated PML based on JC virus antibody index values. The risk appears to be highest in patients with an index value > 1.5. For those patients who have an index value < 0.9, risk appears to be similar to that of a JC virus antibody-negative patient. The study also demonstrates that the index value remains stable over a duration of 18 months. This risk stratification, based on index values, does not appear to be helpful in patients with prior immune suppression.

Limitations of this study include the relatively small number of patients with PML, the lack of association between the index and patients with prior immune suppression, and the short duration of follow up. However despite these limitations, the index value provides another tool to better stratify the risk of PML associated with natalizumab treatment. These findings should be further corroborated with a larger number of patients and longer duration of follow up. ■

ABSTRACT & COMMENTARY

Anti-Titin Antibodies in Myasthenia Gravis

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: Anti-titin antibodies are common in late-onset myasthenia gravis and have a high predictive value for the presence of thymoma in early-onset myasthenia gravis.

SOURCE: Szczudlik P, et al. Antititin antibody in early- and late-onset myasthenia gravis. *Acta Neurol Scand* 2014:130:229-233.

In addition to autoantibodies directed against the acetylcholine receptor (AchR) and the receptor-associated protein muscle-specific tyrosine kinase (MuSK) patients with myasthenia gravis (MG) demonstrate a host of other antibodies. Anti-striated muscle antibodies, present in 30% of MG and reported in 80% of those with thymoma, are associated with late onset and more severe disease, and react with epitopes on muscle proteins including titin, ryanodine receptor, and the voltage-gated potassium channel Kv1.4. Antibodies to titin may be helpful in predicting disease prognosis, but prior reports have offered contradictory results.

Antibodies to titin were measured among a cohort of 295 consecutive MG patients, 188 women and 107 men, ages 12-89 years, seen at the Department of Neurology, Medical University of Warsaw, Poland, between May 2009 and May 2012. Diagnosis was based on the presence of fluctuating weakness affecting oculobulbar, respiratory, or limb muscles, and was confirmed by radioimmunoassay antibody (AchR or MuSK) or electrodiagnostic testing. Congenital MG patients were excluded. Symptom severity was measured using the Myasthenia Gravis Functional Assessment (MGFA) scale, and a complete history of treatments received, frequency of myasthenic crises and remissions, and clinical outcomes were noted. Statistical analysis included the Shapiro-Wilk and Wilcoxon rank-sum tests, and Chi-squared and Fisher's exact tests, with $P < 0.05$ considered significant.

Early-onset MG, defined as onset ≤ 50 years, occurred in 56% (n = 164) of patients and was predominantly female, with 44% (n = 131) experiencing late-onset MG (after age 50), consisting predominantly of men. Peak onset of MG occurred in the third decade in patients with early MG and in the seventh decade in late MG. AChR and MuSK antibodies were present in 92% (n = 271) and 1% (n = 3) of all patients, respectively, with 27% (n = 81) of all MG patients demonstrating anti-titin positivity, all of whom had seropositive MG. Twenty-six patients had thymoma. Early-onset patients were anti-titin positive in 6%, compared to 54% of late-onset MG, but thymoma was present in all early-onset, male, anti-titin positive

patients. Anti-titin positivity was significantly associated with bulbar symptoms in early-onset MG, but not late-onset MG, but it did not significantly differ among ocular MG patients across age groups. Neither risk of crisis, use of immunosuppressive medication, nor more severe MGFA class of MG correlated with anti-titin antibodies. Anti-titin antibodies have a high predictive value for thymoma in early-onset MG, but cannot predict disease severity.

■ COMMENTARY

Among the 6-12% of MG patients who are seronegative for both AChR and MuSK antibodies, a variable proportion (2-50%) have antibodies against low-density lipoprotein receptor-related protein 4 (LRP4), which disrupts AChR aggregation by inhibiting the interaction of agrin-LRP4-MuSK. Approximately 10-15% seronegative MG will have antibodies directed against agrin, an extracellular matrix protein that is a ligand of LRP4, activates MuSK, and is essential for AchR aggregation, whereas almost 20% will have antibodies directed against cortactin, a protein concentrated at the neuromuscular junction that regulates actin polymerization and promotes AchR clustering downstream from agrin/MuSK. Cortactin antibodies are found in fewer than 5% of seropositive MG patients. Further investigations will surely disclose additional antibodies in most, if not all, cases of hitherto seronegative MG. ■

ABSTRACT & COMMENTARY

Intravenous Calcitonin Gene-Related Antibodies for the Prevention of Migraine

By Dara Jamieson, MD

Assistant Professor of Clinical Neurology, Weill Cornell Medical College

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

SYNOPSIS: In a Phase 2 trial, antibodies to calcitonin gene-related peptide resulted in a significant decrease in migraine days measured from baseline to weeks 5 to 8 after one intravenous infusion of the medication, as compared to a placebo infusion. But the high-rate of placebo response (50%) warrants caution in the interpretation of the study results and requires more investigation.

SOURCE: Dodick DW, et al. Safety and efficacy of ALD403, an antibody to calcitonin gene-related peptide, for the prevention of frequent episodic migraine: A randomised, double-blind, placebo-controlled, exploratory phase 2 trial. *Lancet Neurol* 2014;13:1100-1107.

Calcitonin gene-related peptide (CGRP) is a neuropeptide that contributes to the intracranial vasodilation and nociceptive activation of the trigeminovascular system that occurs with migraine. In this randomized, double-blind, placebo-controlled, exploratory, proof-of-concept Phase 2 trial, ALD403, a genetically engineered humanized antibody to CGRP, was assessed for safety and efficacy in migraine prevention. Alder Biopharmaceuticals was the sponsor of the study and took responsibility for the collection, processing, and reporting of the data. Adults with monthly episodic migraine were randomly assigned to receive a 1-hour intravenous infusion of ALD403 1000 mg or of placebo.

The primary efficacy endpoint was the change in the frequency of migraine headache days from baseline to weeks 5 to 8 after infusion, although patients were followed for up to 24 weeks after the one-time infusion. Of the 174 patients randomized at 26 centers in the United States, 163 eventually received either ALD403 (n = 81) or placebo (n = 82). Five patients in the ALD403 group and two patients in the placebo group were lost to follow-up during study. The mean change in migraine days between baseline and weeks 5 to 8 after infusion was -5.6 (SD 3.0) in the ALD403 group, as compared with -4.6 (3.6) in the placebo group (difference -1.0; 95% confidence interval, -2.0 to 0.1; one-sided P = 0.0306). For all time points from the date of infusion and for all percentages of reduction in migraine headache days, the ALD403 treatment group had numerically higher response rates, generally around 20% higher than the placebo treatment group response rate. Of the 143 patients who were able to complete the required electronic headache diary consistently, 11 out of 67 patients treated with ALD403 and none of the 76 patients treated with placebo were 100% migraine free for weeks 1 to 12 of the study. The placebo response rates were high, especially in the 50% migraine-free responder group where the placebo response rate was 50% at 1 to 4 weeks, increasing to 67% at 9 to 12 weeks. Adverse events were experienced by 46 (57%) of 81 patients in the ALD403 group and 43 (52%) of 82 patients in the placebo group. The most frequent adverse events were upper respiratory tract and urinary tract infections, fatigue, back pain, arthralgias, and nausea and vomiting. Six serious adverse events in three patients were judged to be unrelated to study drug. There were no differences in vital signs or laboratory safety data

between the two treatment groups. Pharmacokinetic assays of ALD403 indicted that the mean maximum concentration occurred 4.8 hours after the start of the 1-hour infusion and that the mean apparent terminal elimination half-life was 27.9 days (range 19.9-46.5). Eleven (14%) of 81 patients in the ALD403 group may have formed anti-ALD403 antibodies during the study.

■ COMMENTARY

CGRP, the current "it" compound in migraine treatment, is the target for both acute and preventive therapy. Oral CGRP receptor antagonists have shown efficacy in Phase 2 and Phase 3 trials for acute abortive treatment and may eventually be the first CGRP-targeted intervention to be approved for use in migraine patients. This trial, reported by Dodick et al, indicates potential for another novel anti-CGRP strategy, with an intravenous infusion every as-yet-to-be-determined number of months for migraine headache prevention. However, adoption of this nascent treatment needs further investigation as these preliminary results come from only 163 patients treated for a relatively short period of time, with a robust placebo response as well. That only 174 patients could be recruited into the study from 26 centers is surprising, given the millions of adults in the United States who suffer from migraine headaches. The research protocol was time consuming, with seven visits to the local study center from screening to 24 weeks after the treatment dose, which may have been burdensome to time-stressed patients. An intravenous infusion for headache

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Neurology [ALERT] **Stroke Alert**

By Matthew E. Fink, MD

Left Carotid Artery Atherosclerotic Plaques Are More Vulnerable than Those in the Right Carotid Artery

SOURCE: Selwaness M, et al. Atheroscerotic plaque in the left carotid artery is more vulnerable than in the right. *Stroke* 2014;45:3226-3230.

Ischemic stroke in the distribution of the carotid arteries has been reported to occur more often in the left carotid distribution than the right, but it is unclear if this is due to the higher sensitivity of diagnosis, due to language dysfunction in the left-sided lesions, or if they are truly more common. Many right hemisphere strokes, if they are small, could be missed because of the subtlety of the clinical presentation. The authors investigated the plaque prevalence, severity, and composition of atherosclerotic lesions in the carotid arteries, and compared the left and the right.

Carotid MRI scanning was performed in 1414 stroke-free participants, older than the age of 45 years, to assess the morphology of any atherosclerotic plaques, specifically to look at the presence of a lipid core, intraplaque hemorrhage, calcification, or fibrous tissue in each carotid artery. Differences between the left and right sides were tested using paired t-tests and a generalized estimating equation analysis. The majority of participants (85%) had bilateral carotid plaques. When unilateral plaques were identified, they were more prevalent on the left side than the right side (67% vs 33%; $P < 0.001$). Plaque thickness was greater on the left, but degree of stenosis did not differ between right and left. Intraplaque hemorrhage was more prevalent on the left compared to the right, whereas calcification occurred more often on the right.

Carotid plaque size and composition are not symmetrically distributed, and there may be more vulnerable plaques that develop in the left internal carotid compared to the right. These observations may explain the difference in prevalence between right and left internal carotid artery distribution ischemic strokes. ■

Patent Foramen Ovale Does Not Confer a Higher Risk of Recurrent Events in Cryptogenic Stroke

SOURCE: Katsanos A, et.al. Recurrent stroke and patent foramen ovale: A systematic review and meta-analysis. *Stroke* 2014;45:3352-3359.

Patent foramen ovale (PFO) is common in both the general population, as well as in patients with cryptogenic stroke, with an estimated prevalence somewhere between 15-35%. Recurrent neurovascular events, both recurrent ischemic stroke as well as transient ischemic attacks, are frequent in these patients but it is not clear whether patients with PFOs have an increased rate of recurrent events compared to those patients who do not have PFOs. Katsanos and colleagues performed a review and meta-analysis of all available prospective studies that reported recurrent cerebrovascular events in patients who were diagnosed with cryptogenic stroke or transient ischemic attacks, and were treated medically. These were then compared to the control ischemic stroke patients who did not have PFOs. Fourteen eligible studies were identified with a total of 4251 patients. Patients with stroke and PFO did not have a higher risk of recurrent stroke/transient ischemic attacks (risk ratio, 1.18; 95% confidence interval, 0.78-1.79; $P = 0.03$). The authors also compared the size of the PFO with the risk of recurrent events and did not find any association.

Based on the available evidence, there does not appear to be an increased risk of recurrent cerebral ischemic events in patients with PFO compared to those without a PFO. ■

prevention is a new treatment paradigm but is less painful than onabotulinum toxin injections every 3 months. The authors speculated that intravenous therapy and the novelty of the therapy might have contributed to the high placebo response. The increase in the placebo response over time after infusion may be due to implementation of lifestyle changes that are known to decrease headache frequency and therapy.

The long half-life of the antibody adds to the challenges of the therapy. Possible teratogenic effects of long-term exposure in a population of women of child-bearing age need to be explored. Migraine patients take multiple medications for headaches and comorbidities, so they should be aware of theoretic drug-antibody interactions. The side effect profile appears promising, but any adverse effect may take time to dissipate. These preliminary results are intriguing. However, more studies, with a much larger number of patients who are treated and followed for a much longer period of time, need to be performed before a visit to an infusion center every few months becomes routine for millions of migraine sufferers. ■

CME QUESTIONS

1. **Which of the following statements is correct regarding Parkinson's disease (PD) diagnosis?**
   a. In clinically uncertain cases, current data support likely usefulness of dopamine transporter (DAT) imaging as an adjunct to clinical diagnosis in distinguishing PD from vascular or drug-induced parkinsonism.
   b. Use of DAT imaging is associated with close to 100% sensitivity and specificity in diagnostic accuracy across the range of parkinsonian disorders.
   c. Clinical diagnosis is associated with close to 100% sensitivity and specificity in diagnostic accuracy across the range of parkinsonian disorders.
   d. Use of DAT imaging distinguishes PD from Parkinson's plus disorders such as multiple system atrophy or progressive supranuclear palsy.
2. **Cortical spreading depression occurs in migraine, traumatic brain injury, ischemic stroke, and subarachnoid hemorrhage.**
   a. True
   b. False
3. **Which of the following statements regarding multiple sclerosis patients is true?**
   a. Natalizumab is effective in the treatment of primary progressive MS.
   b. Natalizumab has no adverse side effects on MS patients.
   c. Natalizumab treatment is associated with a long-term risk of PML.
   d. Beta-interferon treatment is associated with a long-term risk of PML.
4. **Which of the following statements is true?**
   a. Cortactin antibodies are found in less than 5% of seropositive myasthenia gravis patients.
   b. Approximately 10-15% seronegative myasthenia gravis patients will have antibodies directed against agrin.
   c. Antibodies directed against low-density lipoprotein receptor-related protein 4 disrupts acetylcholine receptor aggregation.
   d. All of the above
5. **Which of the following statements about calcitonin gene-related peptide (CGRP) is true?**
   a. CGRP causes vasoconstriction in patients with migraine.
   b. Intravenous injection with antibodies to CGRP decreases the severity and duration of a headache attack.
   c. Intravenous injection with antibodies to CGRP decreases the frequency of migraines, as compared to placebo.
   d. CGRP appears to be a therapeutic target only of use for headache prevention.
   e. CGRP targeted therapy is generally poorly tolerated by migraine patients.
6. **Patients with ischemic stroke and a patent foramen ovale (PFO) have a higher risk of recurrent stroke than patients without a PFO.**
   a. True
   b. False
7. **Carotid-territory ischemic strokes occur more often on the left than the right and may be due to a higher prevalence of vulnerable carotid artery plaques on the left.**
   a. True
   b. False

[IN FUTURE ISSUES]

Update on Alzheimer's Disease