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Neurology [ALERT®]

Evidence-based summaries of the latest clinical neurology research

ABSTRACT & COMMENTARY

Blood-brain Barrier Breakdown in RCVS

By Alexander E. Merkler, MD

Assistant Professor of Neurology, Weill Cornell Medical College

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

SYNOPSIS: In this single-center, prospective trial, patients with reversible cerebral vasoconstriction were found to have evidence of blood-brain barrier breakdown on MRI.

SOURCE: Lee MJ, Cha J, Choi HA, et al. Blood-brain barrier breakdown in reversible cerebral vasoconstriction syndrome: Implications for pathophysiology and diagnosis. *Ann Neurol* 2017;81:454-466.

Reversible cerebral vasoconstriction (RCVS) is a clinical and radiographical syndrome characterized by recurrent thunderclap headache and evidence of reversible luminal narrowing of the cerebral vasculature. RCVS is recognized as the most common cause of thunderclap headache and is commonly triggered by everyday medications such as selective serotonin reuptake inhibitors, nasal decongestants, or the puerperium state.[1] Although the vasoconstriction is reversible, complications are common and include ischemic stroke, intracranial hemorrhage, seizures, or death. The underlying pathophysiology of RCVS is poorly understood, but is thought to comprise of dysautoregulation, sympathetic over-activity, and blood-brain barrier (BBB) breakdown. Furthermore, the diagnosis of RCVS often is challenging, as vessel imaging may be normal given the dynamic nature of the disease. In this prospective, single-center study, contrast-enhanced fluid-attenuated inversion recovery (CE-FLAIR) MRI was used to evaluate for BBB breakdown in patients with RCVS and to investigate its role as a novel diagnostic tool. The study enrolled all patients who presented to Samsung Medical Center between 2015-2016 with thunderclap headache. Patients with aneurysmal subarachnoid hemorrhage or contraindication to MRI with gadolinium were excluded. All patients underwent brain MRI with CE-FLAIR within seven (most within two) days of thunderclap headache. Patients were classified as having definitive or probable RCVS according to the International Classification of Headache Disorders-3 beta, in which definite cases had imaging evidence of vasoconstriction and probable cases had supporting

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clinical features of RCVS without imaging evidence of vasoconstriction.[2]

Of 72 patients with thunderclap headache, 41 had RCVS (29 definite and 12 probable), seven patients had a secondary cause of thunderclap headache (i.e., ruptured cavernous malformation), and 24 had thunderclap headache of undetermined cause. BBB breakdown was present in 20 (69.0%) patients with definite RCVS, three (25.0%) patients with probable RCVS, three (12.5%) patients with thunderclap headache of undetermined cause, and no patients with a secondary cause of thunderclap headache. CSF was normal in all patients who had evidence of BBB breakdown. Patients with BBB were more likely to have evidence of vasoconstriction ($P < 0.010$) and were more likely to have multiple vessel involvement ($P < 0.012$). However, visible vasoconstriction was not always associated with BBB breakdown within the corresponding territory. BBB breakdown frequently was multifocal and most commonly found along the falx or superficially. If BBB breakdown was incorporated into the diagnosis of RCVS, 15/36 (41.7%) patients without a secondary cause of thunderclap headache and normal neuroimaging could have been classified as having RCVS.

Neurological complications, including seizures, posterior reversible encephalopathy syndrome, ischemic stroke, or subarachnoid hemorrhage, were uncommon and occurred in only six patients with RCVS (none in patients with secondary thunderclap headache or thunderclap headache of undetermined cause). All patients with neurological complications had evidence of BBB breakdown, and BBB breakdown was independently associated with the occurrence of a neurological complication (odds ratio, 1.48; 95% confidence interval, 1.04-2.12).

■ COMMENTARY

This is the first study to demonstrate that radiographic evidence of BBB breakdown occurs in patients with RCVS. As RCVS often poses a diagnostic challenge, particularly early in its course when angiography may be normal, CE-FLAIR MRI may prove to be a non-invasive tool that may aid in the diagnosis of RCVS.

The study is limited by the fact that it was a single-center study performed exclusively in Asian patients who are prone to intracranial atherosclerosis and potentially greater BBB breakdown. In addition, neurological complications were infrequent and, therefore, the effect of BBB breakdown as a predictor for neurological complications is uncertain.

Overall, this study provides preliminary radiographic evidence of BBB breakdown in patients with RCVS. It remains unclear whether BBB breakdown leads to vasoconstriction or, on the contrary, vasoconstriction leads to BBB breakdown. In either case, if replicated, CE-FLAIR MRI may prove to be a useful adjunct test for the diagnosis of RCVS. ■

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ABSTRACT & COMMENTARY

Rituximab for 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: In uncontrolled, observational case series, rituximab treatment for myasthenia gravis appears to be effective and safe, but more studies are needed for confirmation.

SOURCE: Stieglbauer K, Pichler R, Topakian R. 10-year-outcomes after rituximab for myasthenia gravis: Efficacy, safety, costs of in-hospital care, and impact on childbearing potential. *J Neurol Sci* 2017;375:241-244.

Isolated case reports have noted the short-term benefit of rituximab (RTX) for myasthenia gravis (MG) refractory to standard immunotherapy, including corticosteroids, azathioprine, cyclosporine, plasmapheresis, and intravenous immunoglobulin. Long-

term outcomes of rituximab on the other hand, including cost, safety, efficacy, and effect on childbearing potential, are less well documented, but are addressed in this paper.

Four patients with MG refractory to standard regimens, including prednisone, azathioprine, cyclosporine, mycophenolate mofetil, and plasmapheresis, were treated with RTX at a dose of 375 mg/m^2 weekly for two weeks. Retreatment, a single infusion of 375 mg/m^2, was based on B-cell counts using flow cytometry, but was spaced further apart when, in 2010, concern for potential complications, including progressive multifocal leukoencephalopathy, were raised. Thenceforth, RTX was given only after signs of clinical worsening developed.

Over a median follow-up of 10.1 years, regular neurological evaluations, including the Quantitative Myasthenia Gravis score, revealed dramatic improvement compared to pre-treatment scores, without the need for additional immunosuppressive medication. Three patients maintained their improvement since 2008, without the need for additional immunosuppression, while the fourth patient required only a single additional RTX infusion over a 6.7-year follow-up. Aside from occasional headaches in two patients, RTX was well-tolerated without severe infections or other adverse events noted. Two women each gave birth to a healthy child, one by vaginal delivery and one by caesarean delivery, after uncomplicated pregnancies, without MG flare. Cost of in-hospital MG patient care over the study period was decreased two- to 10-fold compared to pre-RTX cost, based on Austria's diagnosis-related group system in which this retrospective study took place. RTX is safe and effective as treatment for refractory MG and, with further study, may emerge as a first-line choice.

■ COMMENTARY

Rituximab, a chimeric monoclonal antibody that depletes B-cells and their precursors, is a genetically engineered IgG1 kappa immunoglobulin produced by Chinese hamster ovary cells in medium containing gentamicin and purified by chromatography, comprising two heavy chains and two light chains, with a molecular weight of 145 kDa. Directed against CD20, the surface transmembrane phosphoprotein of B-lymphocytes, the Fab domain of RTX binds to CD20, while the Fc domain recruits immune effector cells for B-cell lysis, resulting in significant reductions, for up to six months, of circulating CD20+ B cells. Approved to treat a host of B-cell disorders, including rheumatoid arthritis, non-Hodgkin B-cell lymphoma, microangiopathic vasculitis, and granulomatosis with polyangiitis, RTX also appears efficacious in autoimmune disorders, such as autoimmune hemolytic anemia, immune thrombocytopenia, pemphigus, and MG that is refractory to standard immunomodulation therapy. In a review of 47 publications of RTX in MG, encompassing 28 single case reports with the remainder reporting two or more patients, totaling 30 childhood-onset and 137 adult-onset MG patients, RTX was well-tolerated and resulted in minimal manifestation disease (MG Foundation of America post-intervention scale) in 44% and pharmacologic/stable remission in 27% overall, with 72% of MuSK+ MG and 30% of AchR+ MG achieving minimal manifestation disease or better. Generally safe and effective, controlled trials hopefully will confirm its value in the neurologic arena.[1] ■

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ABSTRACT & COMMENTARY

Fludrocortisone for Orthostatic Hypotension Associated with Parkinson's Disease

By Harini Sarva, MD

Assistant Professor of Clinical Neurology, Weill Cornell Medical College; Assistant Attending Neurologist, NewYork Presbyterian Hospital

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

SYNOPSIS: This double-center, double-blind, randomized, controlled trial compared the efficacy of pyridostigmine bromide vs. fludrocortisone and demonstrated that pyridostigmine bromide was not as effective as fludrocortisone. The authors also provided evidence for the efficacy of fludrocortisone in treating neurogenic orthostatic hypotension.

SOURCE: Schreglmann SR, Buchele F, Sommerauer M, et al. Pyridostigmine bromide versus fludrocortisone in the treatment of orthostatic hypotension in Parkinson's disease. *Eur J Neurol* 2017;24:545-551.

This double-center, double-blind, randomized, controlled trial compared the efficacy of pyridostigmine bromide (PB) with fludrocortisone for orthostatic hypotension (OH) in Parkinson's disease (PD). It was a Phase II, non-inferiority trial. Patients aged 50-80 years with a diagnosis of PD according to the UK Brain Bank Criteria and symptomatic OH (systolic blood pressure [SBP] drop by ≥ 20 mmHg or diastolic blood pressure [DBP]

drop by ≥ 10 mmHg within three minutes of standing). Patients on medications that regulate blood pressure, with systemic diseases such as diabetes mellitus, or with clinical features of cerebellar involvement or multiple system atrophy (MSA) were excluded. The two trial arms were 14 days' duration and the subsequent washout was 21 days prior to crossover. Visits were conducted immediately before drug initiation and immediately after the final dose. The following were performed on the subjects: UPDRS Part III for motor assessment, Montreal Cognitive Assessment, Hospital Anxiety and Depression Scale, Zurich autonomic questionnaire, Orthostatic Hypotension Severity Assessment, non-invasive central blood pressure measures using pulse wave analysis by applanation tonometry, and cardiovascular monitoring using the Schellong maneuver. Home blood pressure in the sitting position consisted of automated repeat morning and evening measurements for seven days. PB was started at 90 mg per day for three days before increasing to 180 mg per day. Fludrocortisone was started at 0.1 mg per day before increasing to 0.2 mg per day after three days. Drug calendars and collection of empty medication boxes were used to assess drug compliance. Thirteen patients were recruited and four dropped out.

After an interim analysis showed futility of PB in comparison to fludrocortisone, the study was stopped and an intent-to-treat analysis was performed. Fludrocortisone improved the primary outcome measure of improvement in DBP drop by 37% as assessed by Schellong maneuver and mean arterial blood pressure standing by 15%, whereas PB had no significant effect. Peripheral SBP supine and SBP home measurements improved by 11% with fludrocortisone, but there was no effect with PB. However, subjective symptom severity did not correlate with the numerical improvements. Although PB lowered central mean supine blood pressure, it remained unchanged with fludrocortisone. Neither had any significant improvement on motor, cognitive, or psychiatric assessments. Transient adverse events were mild for each drug and did not cause study dropout.

■ COMMENTARY

Orthostatic hypotension remains a major quality-of-life issue for patients with PD. Although conservative measures are tried prior to starting medications such as fludrocortisone, midodrine, and now droxidopa, consensus on which medication to choose and dosing still remains an issue. Much of the evidence for using these medications comes from relatively small studies with subjects having various causes of neurogenic orthostatic hypotension, such as MSA and pure autonomic failure. Difficulty in recruitment along with various means of measuring blood pressure changes remain major challenges to defining precise algorithms. In addition, the pathological mechanisms of developing OH in the various conditions is different. In MSA, the lesion site is central and preganglionic, whereas in PD it is peripheral and postganglionic, further adding to the complexity of OH and developing consensus management strategies. In addition, difficulty in accurately measuring central blood pressure changes and their role in accurately predicting vascular response to treatments of orthostatic hypotension have not been well-studied in PD.

This study is important in that it shows that fludrocortisone is effective in treating OH in PD, albeit in a small sample size, and that it may not increase central blood pressure, suggesting that it is a relatively safe treatment. However, the small sample size and the relatively large dropout rate are major limitations of this study. Further evidence is required to first set up consensus accurate BP measurements in PD patients and then to provide an appropriate treatment algorithm. For now, it is still important to exhaust conservative measures, such as increasing salt and fluid intake, using compression stockings, reducing antihypertensives, and possibly adjusting the dose of dopaminergic medications, before initiating blood pressure-raising medications. Anecdotally, we know that improving OH can improve motor and cognitive symptoms, and further research in this area also is needed to determine when blood pressure support should be initiated to improve quality of life and functionality. ■

ABSTRACT & COMMENTARY

Bright-light Therapy for Daytime Sleepiness in Parkinson's Disease Patients

By Daniel A. Barone, MD, FAASM

Assistant Professor of Neurology, Weill Cornell Medical College

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

SYNOPSIS: Light therapy has been shown to be beneficial in treating excessive daytime sleepiness in Parkinson's disease patients and also may improve sleep quality.

SOURCE: Videnovic A, Kierman EB, Wang W, et al. Timed light therapy for sleep and daytime sleepiness associated with Parkinson disease: A randomized clinical trial. *JAMA Neurol* 2017; 74:411-418.

Parkinson's disease (PD), which affects more than 1 million people in the United States, is the second most common neurodegenerative disorder. Although it is known for the classic tetrad of motor symptoms including bradykinesia, tremor, rigidity, and postural instability, sleep disturbances are common as well. For example, excessive daytime sleepiness (EDS) and nocturnal sleep fragmentation affect up to 90% of patients with PD. There is currently a paucity of available treatments for the sleep abnormalities noted in PD patients, and as the authors of this paper reported, there is a great need to develop nonpharmacological approaches to prevent and manage sleep disorders in these patients.

The cause of sleep disturbances in PD patients is attributed to the symptoms of PD itself, the adverse effects of medications, a primary neurodegeneration of central sleep regulatory areas, and disruption of circadian rhythms. Circadian rhythms are generated by a pacemaker located in the suprachiasmatic nucleus of the hypothalamus and produce endogenous physiologic cycles that occur approximately every 24 hours. Social and environmental cues help synchronize the circadian rhythms, and light is the most effective *zeitgeber* (time-giver) of the circadian system.

Bright light has beneficial effects on sleep quality and daytime vigilance in healthy older people and patients with dementia, and has been applied in a variety of sleep and neuropsychiatric conditions. While a few preliminary studies found significant improvements in depression, bradykinesia, rigidity, dyskinesias, and insomnia symptoms with supplemental light exposure in PD, this study was designed to assess the safety and efficacy of light therapy as a novel treatment approach to excessive daytime sleepiness associated with PD.

To accomplish this, the authors randomized participants with PD who had concomitant EDS to receive either bright light therapy (10,000 lux) or dim-red light (control condition, < 300 lux) for 14 days, twice daily. The study was performed in PD centers at Northwestern University and Rush University, and included participants with PD receiving stable dopaminergic therapy with coexistent EDS, as assessed by an Epworth Sleepiness Scale score of ≥ 12, and without cognitive impairment or a primary sleep disorder.

A change in the Epworth Sleepiness Scale score was the primary outcome measurement comparing bright light therapy with dim-red light therapy. The Pittsburgh Sleep Quality Index score, the Parkinson's Disease Sleep Scale score, the visual analog scale score for daytime sleepiness, and sleep log-derived and actigraphy-derived metrics were considered secondary outcome measures.

Sixty-three patients were assessed for eligibility, but 32 were excluded for either refusing to participate (18) or failing to meet inclusion criteria (14). Among the 31 patients (13 males and 18 females; mean [SD] disease duration, 5.9 [3.6] years), 16 (mean age 62.31 [10.83] years of age, eight women) were randomized to receive bright light therapy, and 15 (mean age 64.07 [8.89] years of age, 10 women) were randomized to receive dim-red light therapy.

Bright light therapy resulted in significant improvements in excessive daytime sleepiness, with mean Epworth Sleepiness Scale scores at baseline of 15.81 (3.10) reducing to 11.19 (3.31) after the intervention. Both bright light and dim-red therapies were associated with improvements in sleep quality, as assessed via mean scores on the Pittsburgh Sleep Quality Index (7.88 [4.11] at baseline reducing to 6.25 [4.27] after bright light therapy, and 8.87 [2.83] at baseline reducing to 7.33 [3.52] after dim-red light therapy). Similarly, the Parkinson's Disease Sleep Scale reduced in both cases (97.24 [22.49] at baseline vs. 106.98 [19.37] after bright light therapy, and 95.11 [19.86] at baseline vs. 99.28 [16.94] after dim-red light therapy).

Bright light therapy also improved several self-reported sleep metrics, including sleep fragmentation, sleep quality, and ease of falling asleep, and was associated with increased daily physical activity as assessed by actigraphy.

Light therapy was well tolerated; within the bright light therapy group, two participants reported one adverse effect each of headache and sleepiness and one participant in the dim-red light therapy group reported itchy eyes. In all cases, the adverse effects resolved spontaneously. Thus, the authors concluded that bright light therapy may be a safe and effective intervention for improving sleep and alertness in patients with PD.

■ COMMENTARY

While it is clear that bright light therapy can be an effective treatment, this study was relatively short and the improvements modest. Furthermore, there are other concerns with bright light therapy; there is a possible association of PD with bipolar disorder, and it is well-known that the use of bright light therapy in patients with bipolar disorder may trigger a manic episode. As with any treatment modality, careful selection of appropriate patients would need to be exercised. Overall, this was a well-designed and executed study. Hopefully, longer-term and more robust trials will shed further light on the tolerability, safety, compliance, and effectiveness of this promising therapy. ■

ABSTRACT & COMMENTARY

Outcomes After Surgical Treatment of Nonlesional Neocortical Epilepsy

By Kimberly Pargeon, MD

Assistant Professor of Clinical Neurology, Weill Cornell Medical College

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

SYNOPSIS: In this study of 109 consecutive patients with medically refractory neocortical epilepsy without MRI-identifiable lesions who underwent focal resection at a single hospital from 1995 to 2005, almost 60% of patients achieved long-term seizure freedom, with anti-epileptic drugs being withdrawn successfully in about a third of these patients.

SOURCE: Kim DW, Lee SK, Moon HJ, et al. Surgical treatment of nonlesional neocortical epilepsy: Long-term longitudinal study. *JAMA Neurol* 2017;74:324-331.

For patients with medically refractory focal epilepsy, epilepsy surgery can be an important therapeutic option. The most successful surgical outcomes typically are seen with mesial temporal lobe epilepsy (mTLE), particularly where the ipsilateral mesial temporal structures appear atrophic with increased signal on MRI. However, in neocortical epilepsy, the same tools used for localizing the epileptogenic onset zone in mTLE can be less helpful, so not surprisingly, patients with MRI-identifiable lesions are offered surgical resection more often than those without and typically with more satisfactory outcomes.[1] Kim et al were interested in the surgical outcomes for patients with medically refractory neocortical epilepsy without MRI-identifiable lesions and in identifying potential prognostic factors.

The authors identified 109 consecutive patients at a single hospital in Seoul, South Korea, with medically refractory neocortical epilepsy without MRI-identifiable lesions who underwent focal surgical resection from 1995 to 2005. Patients consisted of 64 males (59%), ranging in age from 7-56 years with an average age of seizure onset of 13.6 years (SD, 7.6 years) and average seizure duration of 13.4 years (SD, 7.3 years). All patients underwent a brain MRI (up to 1.5T), and most patients underwent a FDG-PET scan (90%) and/or a SPECT scan (65%, both ictal and interictal). All patients underwent interictal and ictal scalp EEG monitoring with additional anterior temporal electrodes, and also later underwent intracranial EEG monitoring with a combination of implanted grids and strips, with placement based on their presurgical evaluation.

Follow-up data were available for at least 10 years for all but one patient. Localizations were as follows: 39 frontal, 44 neocortical temporal, 12 parietal, 13 occipital, and one multifocal. The most common pathological finding was focal cortical dysplasia in 60%, followed by nonspecific gliosis (13%). At one year post-surgery, 54.1% achieved seizure freedom (Engel class I) with an additional 33.9% achieving a "worthwhile" improvement (Engel class II or III). There were no significant changes at 10 years, with 59.3% reporting seizure freedom and an additional 30.6% achieving a worthwhile improvement. Of the patients achieving seizure freedom at 10 years, all anti-seizure medications were withdrawn successfully without seizure recurrence in 35.9% at last follow-up.

The authors also looked at prognostic factors that may predict better surgical outcomes. On univariate analysis, localizing patterns on other imaging tests (FDG-PET and ictal SPECT), "high" concordance in noninvasive presurgical evaluations, and complete resection of the region of ictal onset on intracranial monitoring were significant prognostic factors at year 1; however, none of these was an independent predictor of seizure freedom in the multivariate analysis. At year 10, presence of aura, higher concordance of presurgical data, and complete resection of the area of ictal onset on intracranial monitoring were significant prognostic factors, with the presence of aura remaining as the only independent prognostic factor on multivariate analysis. Findings were comparable at last follow-up, except complete resection of the region of ictal onset also was an independent prognostic factor on multivariate analysis.

■ COMMENTARY

In cases of medically refractory focal epilepsy, the ultimate goal is to offer patients potentially curative surgery. However, we often struggle with how to identify which patients may be the most "ideal" candidates and how to predict the likelihood of seizure freedom for individual patients. Kim et al attempted to address these issues for a group of patients many neurologists have determined are poor surgery candidates. However, now that the cases of typical mTLE have declined, we are looking for other groups of patients in whom we can intervene surgically. In fact, a recent study showed that the annual rate of anterior temporal lobectomies for mesial temporal sclerosis decreased by more than 65% between 2006 and 2010 at level 3 and 4 epilepsy centers in the United

States, with the annual rate of extratemporal surgery exceeding that for MTS as of 2008.[1] Kim et al found that approximately 60% of patients with nonlesional neocortical epilepsy had long-term seizure freedom after resection at last follow-up, with about a third of those patients tolerating withdrawal of all anti-seizure medications without seizure recurrence. Another 30% of patients had some "worthwhile" improvement (Engel class II or III) at last follow-up. However, it should be noted that this study included a small number of patients at a single center. Although the follow-up period was prolonged at a minimum of 10 years, these findings are not reflective of newer, more modern diagnostic or surgical techniques, such as stereo EEG or more powerful MRIs (e.g., 3T). It may be reasonable to presume that these techniques only would improve the chances of success for future patients. ■

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ABSTRACT & COMMENTARY

A Novel Target for Migraine Prevention Through Modulation of Stress Receptors

By Dara Jamieson, MD

Associate Professor of Clinical Neurology, Weill Cornell Medical College

Dr. Jamieson reports she is a consultant for Roche.

SYNOPSIS: Kappa opioid receptors (KORs) modulate response to stress, a common migraine trigger, so KOR blockade may be a novel preventive treatment for migraine as well as other stress-related diseases.

SOURCE: Xie JY, De Felice M, Kopruszinski CM, et al. Kappa opioid receptor antagonists: A possible new class of therapeutics for migraine prevention. *Cephalalgia* 2017; Jan 1:333102417702120. doi: 10.1177/0333102417702120. [Epub ahead of print].

Stress, or relief from stress, is one of the most commonly reported migraine triggers, but the mechanism underlying the correlation is poorly understood. Kappa opioid receptors (KORs), present in multiple structures in the cerebrum and brainstem, are involved in the modulation of reward-seeking behavior, mood disorders (including anxiety and depression), and cognitive functioning. Dynorphin, an endogenous opioid peptide that is a potent modulator of pain response and stress behavior, interacts with KORs. This study used an "injury-free" rodent model to test the preventive effect of KOR blockade on stress-induced cephalic pain. Excessively frequent use of an acute pain medication for migraine (i.e., a triptan) in rats was used to develop a medication overuse headache (MOH) model that simulated an increased frequency of migraine attacks. Using surgically implanted minipumps, rats were primed with sumatriptan, causing a state of "latent sensitization" characterized by the presence of multiple known migraine markers, including increased trigeminal ganglion cells that expressed the migraine-related neuropeptide calcitonin gene-related peptide (CGRP), increased sensitivity to migraine triggers, stress-induced cutaneous allodynia, and increased levels of CGRP detected in jugular blood. The role of CGRP blockade in migraine treatment is well known since stress-induced cephalic (i.e., periorbital) and extracephalic (i.e., hind-paw) allodynia in rats with prior exposure to sumatriptan is blocked by CGRP antibodies. After priming with sumatriptan for seven days, followed by a 14-day, drug-free period, the rats then underwent two days of an hour-long exposure to bright light as an environmental stressor used to trigger a migraine response. Markers of migraine in the rat (i.e., allodynia, tail-flick test, and intrajugular CGRP), in addition to neurochemical (plasma CGRP release, dynorphin, KOR phosphorylation) and immunohistochemical (KOR phosphorylation) markers of environmental stress, were assessed in the presence or absence of systemic or intra-amygdala blockade of KOR signaling. The stressor of bright light exposure resulted in a significant elevation of dynorphin levels and in the activation and phosphorylation of the KOR receptors in the bilateral central nuclei of the amygdala (CeA) of sumatriptan-primed rats, as compared to saline-primed rats. Long-acting (nor-binaltorphimine) or short-acting (CYM51317) KOR antagonists were given systemically either during the sumatriptan priming period or immediately before the bright-light stress challenge. Systemic KOR blockade prevented both the migraine physiological markers of stress-induced allodynia and the increased plasma CGRP. Oral administration of CYM51317 blocked stress-induced periorbital and hind-paw cutaneous allodynia. The long-acting KOR antagonist was injected into the right or the left CeA with a lateralized therapeutic effect. Nor-binaltorphimine injection in the right, but not in the left, CeA blocked bright light stress-induced cutaneous allodynia, regardless of whether extracerebral allodynic thresholds were measured in the right or the left hind-paws.

■ COMMENTARY

Xie et al developed a sumatriptan-primed rat model, overlapping migraine and triptan-associated MOH, and used the model to test the hypothesis that modulation of KORs could mediate the migraine markers of stress-induced cutaneous allodynia and increased plasma CGRP. They discovered a lateralized effect of the antagonism of the KOR circuit as blockade of KOR signaling in the right, but not left, CeA-inhibited, stress-induced cephalic and extracephalic allodynia. The authors suggested that this dynorphin/KOR signaling pathway in the right CeA may modulate stress responses, including migraine triggering. A prior observation that the right, but not the left, amygdala appears to be activated in pain states may explain the laterality in this stress-mediating circuit. There are restrictions to this model that it does not ideally replicate migraines, as the sumatriptan-priming trigger also mirrors MOH. However, the response to the bright light stress stimulus appeared to produce physiological stress and migraine. Migraine is too complicated to be prevented by a single mechanism or circuit blockade, as evidenced by the many different categories of preventive medications (e.g., seizure, blood pressure, and antidepressant medications) and the multitude of techniques used for prevention with relatively disappointing success. Currently, antibodies to CRGP are being evaluated in human clinical trials as a parenteral preventive migraine medication. Whether prevention of migraine in the future uses a cocktail of many medications or a precision medicine approach predicting the individual patients response to a particular treatment, more effective medications are necessary. Exploration of new therapeutic targets for the acute or preventive treatment of migraine is crucial. Based on current animal models, KOR antagonists, especially if orally effective, may represent an ideal novel class of medications for migraine prevention. Only further investigation with animal models and human clinical trials will determine whether the KOR circuit is a viable therapeutic target for migraine prevention or just an interesting mirage. ■

CME QUESTIONS

1. **A 43-year-old postpartum woman presents to the emergency department after experiencing a sudden onset thunderclap headache the day before. Her head CT is normal. Which of the following tests should be performed next?**
   a. Brain MRI without contrast
   b. Contrast-enhanced fluid-attenuated inversion recovery (CE-FLAIR)
   c. Lumbar puncture
   d. CT angiography
   e. Digital subtraction angiography

2. **Which of the following is true of rituximab for refractory myasthenia gravis?**
   a. Initially, it may be given at a dose of 375 mg/m^2 weekly for two weeks.
   b. Retreatment may be based on B-cell counts using flow cytometry or clinical deterioration.
   c. It is a chimeric monoclonal antibody that targets the CD20 antigen found on B-lymphocytes.
   d. All of the above

3. **Which of the following is true regarding fludrocortisone in comparison with pyridostigmine bromide?**
   a. It reduced mean arterial blood pressure standing.
   b. It improved mean diastolic blood pressure drop by 15%.
   c. It improved diastolic blood pressure drop by 37%.
   d. It increased central blood pressure measurements.

4. **Bright-light therapy has been shown to be beneficial in all but which of the following disorders?**
   a. Depression
   b. Mania
   c. Excessive daytime sleepiness
   d. Insomnia
   e. Jet lag

5. **At the 10-year follow-up, what was the only independent prognostic factor for seizure freedom?**
   a. Area of ictal onset on intracranial EEG
   b. Presence of aura
   c. High concordance of presurgical data
   d. Localizing patterns on other imaging studies

[IN FUTURE ISSUES]

The Latest Regarding Alzheimer's Disease