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Neurology [ALERT®]

Evidence-based summaries of the latest clinical neurology research

ABSTRACT & COMMENTARY

Randomized Trial of Cannabidiol for Medically Refractory Seizures in Dravet Syndrome

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 a double-blind study, 120 children and young adults with the Dravet syndrome and medically refractory seizures were assigned randomly to receive either cannabidiol or placebo, as well as their usual antiepileptic drugs/therapies. The primary finding was a significant decrease in convulsive seizure frequency during the 14-week treatment period for patients receiving cannabidiol compared to those receiving placebo.

SOURCE: Devinsky O, Cross JH, Laux L, et al. Trial of cannabidiol for drug-resistant seizures in the Dravet syndrome. *N Engl J Med* 2017;376:2011-2020.

Currently, there are no approved medical treatments for Dravet syndrome (DS), a childhood epileptic encephalopathy.[1] Typically, DS is caused by mutations in the *SCN1A* gene, resulting in seizures starting at around age 6 months, usually in the context of high fever, often after initially normal development. Seizures can become medically refractory and children can show neurological regression, often with significant developmental delay, and are at risk for early death.[2] Families can be frustrated by failed treatment with polypharmacy using current antiepileptic drugs (AEDs) leading to frequent side effects.[1] Medical marijuana (MMJ) is a popular topic for the media and patients alike, particularly for those seeking "natural" treatments or for patients and families in desperate need of a "magic bullet" for devastating drug-resistant seizures. Unfortunately, until recently, available information for clinicians has been limited to case reports, case series, or inconclusive trials in varied populations.[1] Based on preclinical data and anecdotal reports, a group

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of clinical investigators and GW Pharmaceuticals collaborated to investigate the safety and efficacy of cannabidiol (CBD) in childhood refractory epilepsies using Epidiolex (100 mg/mL CBD).[1]

This was a double-blind, placebo-controlled trial in which children and young adults with confirmed DS and medically refractory seizures were assigned randomly to receive CBD at 20 mg/kg/day or placebo in addition to their usual AEDs. The study was conducted at 23 centers in the United States and Europe, with 120 subjects undergoing randomization (61 CBD, 59 placebo). Subjects ranged in age from 2-18 years (mean 9.8 years) and 52% were male. All treatments were stable for four weeks prior to randomization and throughout the trial, which began with a four-week baseline period, during which baseline seizure frequency was determined (eligibility required four or more seizures). This was followed by a 14-week treatment period, during which CBD or placebo was escalated to 20 mg/kg/day over 14 days and then maintained for 12 weeks. This was followed by a 10-day taper and then a four-week follow-up period. After trial completion, subjects could enter an open-label study.

Ninety percent of subjects completed the treatment period (52/61 CBD vs. 56/59 placebo). Subjects previously had tried a median of 4.0 AEDs, most commonly clobazam, valproate, stiripentol, levetiracetam, and topiramate. Baseline convulsion frequency was a median of 13.0 seizures per month, the most common type being generalized tonic-clonic (78%). Nearly all subjects had some degree of developmental delay, with nearly half (48%) having "severe or profound" disability.

The primary endpoint was change in convulsive seizure frequency from baseline. There was a decrease from a median of 12.4 seizures/month at baseline to 5.9 seizures/month (-38.9%) in the CBD group, as compared to a decrease from 14.9 seizures/month at baseline to 14.1 seizures/month in the placebo group (-13.3%). The adjusted median difference was -22.8% ($P = 0.01$). For secondary endpoints, the percentage of subjects with at least a 50% reduction of convulsive seizures was 43% and 27% for the CBD and placebo groups, respectively ($P = 0.08$). Although the frequency for all seizure types in the CBD group was significantly reduced compared to the placebo group ($P = 0.03$), there was no significant reduction for non-convulsive seizures. Five percent of the CBD patients were seizure free for all seizure types, but none were seizure free in the placebo group ($P = 0.08$). Patients' overall condition improved, measured by a caregiver scale, in 62% of the CBD group compared to 34% of the placebo group ($P = 0.02$). However, more side effects were reported in the CBD group (93% vs. 75%), most rated mild to moderate (89%). Most adverse events (75%) were attributed to the trial agent and included diarrhea, vomiting, fatigue, somnolence, pyrexia, and abnormal liver function tests. More trial withdrawals due to adverse events occurred in the CBD group (8 vs. 1).

■ COMMENTARY

Up to one-third of patients with epilepsy will be medically refractory, especially those with epileptic encephalopathies, such as DS, for which there is no approved medical treatment.[1] Patients often are treated incompletely with multiple AEDs, leading to negative side effects. Although MMJ has gained recent popularity, until recently, we had only limited or anecdotal evidence for the efficacy of MMJ, with little empiric data related to safety and proper dosing. Although more than half of states and the District of Columbia have approved MMJ programs, the available forms and modes of administration vary.[1] By using a randomized, controlled design, Devinsky et al finally have provided prospective empiric evidence supporting the specific use of CBD at 20 mg/kg in children and young adults with DS for significant reduction of convulsive seizures, which potentially could reduce the risk for convulsion-related complications, such as status epilepticus and sudden unexpected death in epilepsy. Future directions should focus on replicating results with DS and other epileptic encephalopathies, as well as for other refractory epilepsies and in other age groups. ■

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2. Berkovic SF. Cannabinoids for epilepsy – Real data, at last. *N Engl J Med* 2017;376:2075-2076.

ABSTRACT & COMMENTARY

Distinguishing the Neuropathy Associated with MGUS from POEMS

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: Nerve conduction and electromyography can help differentiate the neuropathy associated with monoclonal gammopathy of undetermined significance (MGUS) from polyneuropathy, organomegaly, endocrinopathy, M-protein, and skin changes (POEMS).

SOURCE: Kim H, Lim YM, Jin JY, et al. Electrophysiological features of POEMS syndrome compared to MGUS-related neuropathy. *Muscle Nerve* 2017; May 4. doi: 10.1002/mus.25684 [Epub ahead of print].

Paraproteinemia, found in approximately 1% of the population, often is associated with demyelinating neuropathy. Most commonly seen with monoclonal gammopathy of undetermined significance (MGUS), paraproteinemic neuropathies also are seen with hematologic malignant and nonmalignant conditions, including lymphoma, multiple myeloma, amyloidosis, and cryoglobulinemia. POEMS, an acronym coined in 1980, represents a constellation of findings, including Polyneuropathy, Organomegaly, Endocrinopathy, Monoclonal protein, and Skin changes, in association with osteosclerotic myeloma, Castleman's disease, increased levels of serum vascular endothelial growth factor, edema, or papilledema. Can MGUS neuropathy be differentiated electrodiagnostically from that seen in POEMS?

In this retrospective study, performed between March 1996 and June 2016 at Asan Medical Center and Ulsan University Hospital, South Korea, records of 37 MGUS and 24 POEMS neuropathy patients were reviewed. MGUS neuropathy was diagnosed based on the presence of a monoclonal protein on immunoelectrophoresis, in the absence of any plasma cell disorder or other cause of polyneuropathy, including diabetes, vitamin deficiency, and metabolic or autoimmune disease. POEMS diagnosis satisfied Dispenzieri criteria.[1] Nerve conduction studies were performed using standard technique, and included the bilateral peroneal, tibial, median, and ulnar motor nerves, and median ulnar and sural sensory nerves. Motor nerve conduction block was diagnosed in the presence of a ≥ 50% proximal:distal drop in amplitude, with the stipulation that distal motor amplitude had to be ≥ 1 mV. Terminal latency index (TLI) was calculated for each motor study, using the formula: TLI = terminal distance (mm)/(distal latency (ms) x MCV (m/s). Statistical analysis encompassed, as appropriate, the Student's t test or Mann-Whitney U test, analysis of variance (ANOVA) or Kruskal-Wallis test, and Chi-square or Fisher's exact test. *P* values < 0.05 were considered statistically significant.

Most patients in both groups were male, but those in the MGUS neuropathy group were older (mean age 69.7 years), with longer disease duration (mean 1.83 years) and higher monoclonal peak compared to the POEMS neuropathy group. POEMS patients had significantly lower evoked motor amplitudes in the arms and legs, with motor responses more frequently absent in the leg, and motor conduction velocities slower in the median and ulnar nerves compared to MGUS patients. Sensory amplitudes were comparably reduced in both groups. F-wave latencies were more prolonged in the upper extremities of POEMS patients compared to MGUS, but conduction block was present equally in both, 6.7% and 7.2%, respectively. TLIs were significantly greater in the POEMS compared to MGUS neuropathy group. Receiver operating curve analysis of nerve conduction parameters revealed a sensitivity and specificity of 67% and 88%, respectively, in discriminating POEMS from MGUS-related neuropathy in the median nerve, and of 73% and 84%, respectively, in the ulnar nerve. Reduced motor amplitudes, slow motor conduction velocities, and high TLIs are indicative of POEMS rather than MGUS neuropathy.

■ COMMENTARY

POEMS may be difficult to distinguish clinically from chronic inflammatory demyelinating polyradiculopathy (CIDP), as both may present with a demyelinating polyneuropathy. POEMS should be considered in CIDP patients who do not respond to standard treatment. Vascular endothelial growth factor levels almost always are elevated in patients with active POEMS, with serum levels 10-50 times higher than plasma levels. M-protein is usually low, rarely > 3.0 g/dL, and usually is IgG or IgA, almost always lambda type. Cerebrospinal fluid protein levels always are elevated and, hence, do not aid differentiating CIDP from POEMS. Osteosclerotic lesions occur in 95% but may be confused with aneurysmal bone cysts, fibrous dysplasia, and benign bone islands. ■

REFERENCE

1. Dispenzieri A. POEMS syndrome: Update on diagnosis, risk-stratification, and management. *Am J Hematol* 2015;90: 951-962.

ABSTRACT & COMMENTARY

Omega-3 Polyunsaturated Fatty Acid Supplementation and Cognitive Decline

By Makoto Ishii, MD, PhD

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

SYNOPSIS: In a randomized, placebo-controlled trial of 1,680 participants aged 70 years or older, there was no significant difference in cognitive decline between any of the intervention groups taking omega-3 polyunsaturated fatty acid supplementation and/or multidomain intervention (physical activity, cognitive training, and nutritional advice) compared to the placebo group. However, exploratory post hoc analyses showed some promise for a protective effect with intervention in certain at-risk subgroups.

SOURCE: Andrieu S, Guyonnet S, Coley N, et al. Effect of long-term omega 3 polyunsaturated fatty acid supplementation with or without multidomain intervention on cognitive function in elderly adults with memory complaints (MAPT): A randomised, placebo-controlled trial. *Lancet Neurol* 2017;16:377-389.

As Alzheimer's disease and related dementia remain incurable, there is significant interest in identifying effective prevention strategies. Previous single-domain intervention trials (e.g., nutritional supplements, cognitive training, physical activity) have found protective effects on cognitive decline, but they remain controversial because of a lack of large-scale, randomized, controlled studies. The Multidomain Alzheimer Preventive Trial (MAPT) is a pioneering large multicenter, randomized, placebo-controlled trial testing whether multidomain lifestyle intervention and polyunsaturated fatty acids, either alone or in combination, could prevent cognitive decline over 36 months.

Between 2008 and 2011, the study enrolled 1,680 participants from 13 memory centers in France and Monaco. Participants were non-demented, aged 70 years or older, community dwelling, and met at least one of the three criteria: spontaneous memory complaint, limitation in one instrumental activity of daily living, or slow gait speed. Exclusion criteria included Mini Mental State Examination (MMSE) < 24, any difficulty in basic activities of living, and taking polyunsaturated fatty acids supplementation at baseline. Subjects were randomly allocated (1:1:1:1) to the combined intervention with multidomain intervention plus polyunsaturated fatty acids supplementation (total daily dose of 800 mg docosahexaenoic acid [DHA] and 225 mg of eicosapentaenoic acid [EPA]), multidomain intervention plus placebo, polyunsaturated fatty acids only, or placebo only. The multidomain intervention consisted of small group sessions focusing on three domains (cognitive stimulation, physical activity, and nutrition) and preventive consultation sessions with a physician to optimize cardiovascular risk factors and detect any functional impairment. The primary outcome of the study was change from baseline to 36 months in a composite Z score combining four cognitive tests (free and total recall of the Free and Cued Selective Reminding Test, 10 MMSE orientation items, the Digit Symbol Substitution Test score from the Wechsler Adult Intelligence Scale-Revised, and the Category Naming Test). Secondary outcomes were the individual components of the composite score, scores on other cognitive tests, and scores on the Short Physical Performance Battery and the Alzheimer's Disease Cooperative Study – Activities of Daily Living Prevention Instrument, Clinical Dementia Rating (CDR), Fried's frailty criteria, and the Geriatric Depression Scale. One hundred fifty-four participants were excluded because of lack of follow-up cognitive assessments, and one participant withdrew consent. Adherence was lower for the multidomain intervention groups with polyunsaturated fatty acids (55%) or with placebo (53%) compared to the polyunsaturated fatty acid (79%) or placebo (85%) alone groups.

In the primary efficacy analyses, there were no significant differences in three-year cognitive decline between any of the three intervention groups and placebo group. In a post hoc analysis, pooled analyses of all participants who received the multidomain intervention had significantly less cognitive decline compared to those who did not ($P = 0.015$), while the cognitive decline was similar between all participants who received the polyunsaturated fatty acids compared to those who did not. For secondary outcomes, the combined intervention group had less of a decline in the 10 MMSE orientation items compared to the placebo group. No differences were seen in the other secondary outcome measures.

In post hoc analyses, participants in the placebo group with low baseline concentrations of DHA and EPA in red blood cells had a significant cognitive decline compared to those in the placebo group with high concentrations of DHA and EPA, whose cognitive performances remained stable, but the interventions did not alter cognitive decline in this subgroup. Additional post hoc subgroup

analyses found participants with a positive amyloid PET scan receiving combined intervention or multidomain intervention plus placebo had less cognitive decline compared to those with a positive amyloid PET scan receiving placebo alone ($P < 0.0001$, $P = 0.003$, respectively).

■ COMMENTARY

As the first large randomized, placebo-controlled trial studying the efficacy of a lifestyle intervention with a nutraceutical compound (polyunsaturated fatty acid), MAPT is a landmark study. The negative results from the primary outcome at first may be seen as a disappointing failure for prevention intervention in dementia; however, the results from this study have yielded important information for designing future prevention trials. Results from recent Alzheimer's disease clinical trials suggest that intervening as early as possible, such as during the pre-symptomatic or preclinical stage may be critical. In MAPT, a significant portion of the study population (~40%) had a CDR of 0.5, which may be too late for preventive intervention. Additionally, exploratory analyses found specific subgroups that had decreased cognitive decline with multidomain intervention, including those individuals with positive amyloid PET scans and those with CAIDE dementia risk score of ≥ 6. Collectively, this suggests that preventive interventions may be most efficacious by targeting those with the highest risk of developing dementia as early as possible. ■

ABSTRACT & COMMENTARY

Migraine and the Blood-brain Barrier

By Dara Jamieson, MD

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Dr. Jamieson reports she is a consultant for Roche.

SYNOPSIS: During spontaneous attacks of migraine with visual aura, magnetic imaging studies indicate that the blood-brain barrier remains intact and the pons is activated.

SOURCES: Hougaard A, Amin FM, Christensen CE, et al. Increased brainstem perfusion, but no blood brain barrier disruption, during attacks of migraine with aura. *Brain* 2017;140;1633-1642.

Moskowitz M. Holes in the leaky migraine blood-brain barrier hypothesis? *Brain* 2017:140;1537-1539.

Focal neurological symptoms precede approximately 20% of attacks of migraine-like head pain. The mechanism of this migraine aura is presumed to be related to cortical spreading depression (CSD), which is the propagation of neuronal depolarization, accompanied by sequential fluctuation in cerebral blood flow (CBF) and alteration in the blood-brain barrier (BBB) leading to efflux of inflammatory neuropeptides. The stimulation of the trigeminovascular system activates brainstem nuclei with triggering and perpetuation of the pain phase of a migraine headache.

The hypothesis of this study was that attacks of migraine with a typical visual aura would be accompanied by an increase in BBB permeability and in-brain hyperperfusion (increased CBF). Dynamic contrast-enhanced high-field (3 T) magnetic resonance imaging was used to measure BBB permeability and tissue perfusion simultaneously in multiple cerebral and brainstem areas during spontaneous attacks of migraine with aura. Eleven females and eight males underwent magnetic resonance imaging after the aura had resolved. No individuals were scanned while actually experiencing the auras, which lasted from 18-60 minutes. Headache intensity during scanning ranged from 0 to 9, with a mean of 4.6 on a 10-point pain scale. One person had an aura without headache. Imaging occurred between one and 22 hours (mean 7.6 hours) after the onset of an aura, that was visual in all subjects and sensory and/or aphasic in five individuals. The authors chose this time period from aura onset to scanning based on animal studies showing BBB breakdown from three hours, with a peak at 24 hours, following CSD. Scanning also was performed on a day remote from the attack of migraine with aura. Ten anatomic regions of interest on imaging were placed in the bilaterally in the calcarine sulci, lower pons, and in periventricular white matter areas in each vascular territory.

There were no statistically significant differences in BBB permeability (Ki) on migraine aura attack days as compared to attack-free days in any of the regions of interest in either the affected or the non-affected hemispheres. Mean CBF values were compared between attack and attack-free days in the 19 individuals with migraine aura. On a migraine attack day, CBF was increased in the calcarine cortex bilaterally, more on the affected side. An increase of CBF also was found in the posterior periventricular white matter only on the side of the affected hemisphere and in the lower brainstem bilaterally, greater on the perceived aura side. No differences in mean brain perfusion on attack and attack-free days were seen in the anterior and middle cerebral artery territories. No correlations were found between changes in Ki or CBF and the clinical measurement of time from symptom onset or headache intensity. The authors concluded that the findings of hyperperfusion in the brainstem after the aura,

with preservation of the BBB, "contradict the preclinical hypothesis of cortical spreading depression-induced blood-brain barrier disruption as a possible mechanism linking aura and headache."

Michael Moskowitz, MD, wrote a commentary on this research emphasizing the historical importance of the BBB in the explanation of migraine pathophysiology and noting that a permeable barrier may both allow noxious chemicals to trigger pain in the brain and facilitate drugs interacting with central nervous system receptors. How then to explain the finding that the BBB is not impaired after an attack of migraine without aura? Dr. Moskowitz noted that the imaging studies did not find disruption of BBB function "within the time window identified on the basis of CSD in an animal model." However, he notes that the disruption of the BBB in human migraine may have a different time sequence, not measured by the current investigation.

■ COMMENTARY

Hougaard et al did not find differences in BBB permeability within hours to a day following a migraine aura, as compared to attack-free days, challenging the association of aura-associated CSD with the breakdown of the BBB. The other notable finding of this study, the activation of the pons during the migraine head pain after the aura, confirms other studies showing brainstem activation and reinforces the importance of brainstem nuclei in the activation and perpetuation of migraine pain.

This study, deflating the importance of the BBB in the pathophysiology of a migraine aura, indicates the complexity of the cascade of events occurring from the onset of the neurological symptoms of an aura to the triggering of head pain. As pointed out by Dr. Moskowitz in his commentary, disruption of the BBB is not necessary for the therapeutic benefit of CNS impenetrable agents, such as some 5-HT1 receptor agonists and CGRP receptor antagonists, in aborting migraine pain. These efficacious agents appear to target sites outside the BBB, decreasing its therapeutic importance in migraine. The timing of the scanning used to detect changes in the BBB may be critical. There are flaws in extrapolating animal models of migraine phenomena on to the human timeline; and serendipitous brain imaging during a migraine event has added immensely to the understanding of migraine pathophysiology. Before completely discounting the role of the BBB in the migraine aura, more imaging studies, with smaller and varied regions of interest, need to be performed during or in closer temporal proximity to the aura. ■

ABSTRACT & COMMENTARY

Deep Brain Stimulation May Offer Hope in Treating Post-stroke Pain

By Harini Sarva, MD

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

SYNOPSIS: This trial of deep brain stimulation of the ventral striatum/anterior limb of the internal capsule improved several measures of the affective sphere of pain in those suffering from post-stroke pain, despite no significant improvement seen in the pain disability index.

SOURCE: Lempka SF, Malone DA Jr, Hu B, et al. Randomized clinical trial of deep brain stimulation for poststroke pain. *Ann Neurol* 2017;81:653-663.

This six-month, double-blind, randomized, placebo-controlled, crossover study followed by an 18-month open-label extension assessed the effects of stimulation of the ventral striatum/anterior limb of the internal capsule (VS/ALIC) in the treatment of post-stroke pain. The primary endpoint was at least a 50% reduction in the pain disability index (PDI) and the secondary endpoints included > 50% improvement in the PDI in 50% of patients at two-year follow up; affirmative response to the prospect of repeating this treatment if the same outcome was possible; and > 50% improvement in the visual analogue scale in 50% of patients at two-year follow up. Inclusion criteria were hemi-body pain and anesthesia dolorosa due to contralateral thalamic or somatosensory pathway lesion, at least six months of medically refractory pain, a PDI score of at least 30 at the time of enrollment, pain severity of > 5 on a 0 to 10 scale, and failure to respond to at least one oral narcotic, one antiepileptic, or one antidepressant. Exclusion criteria were severe psychiatric or cognitive comorbidities and contraindications to DBS. After assessing 69 patients, 10 were included, but eventually nine were randomized as follows: four to the DBS "off" group and five to the DBS "on" group for three months with subsequent crossing over of each group. Five of the nine patients continued the open-label extension for 18 months. Various neuropsychiatric tests were performed at one, two, and three months during the randomization phase. The average age of the patients

was 51.3 years, mean time since stroke 4.7 years, and the mean pain intensity was 8.5 out of 10 on a 0 to 10 scale. The randomization phase did not reveal significant differences in the PDI, but those receiving active stimulation had significant improvements in the Beck Depression Inventory, McGill Affective Pain Rating Scale, Montgomery–Asberg Depression Rating Scale, and the McGill Present Pain Scale. At the end of the open label extension, about one-third of total participants continued to report a positive response on these affective scales. The participants were able to predict correctly whether they were being stimulated during the randomization phase at a significantly higher rate than chance. Lastly, when asked if they would have the procedure again despite the same results, five of nine responded positively. Serious adverse events, such as wound dehiscence and infection, resolved.

■ COMMENTARY

Post-stroke pain significantly affects quality of life and is very challenging to treat. Standard treatments with narcotics, antidepressants, antiepileptics, physical therapy, and botulinum toxin are limited either by side effects or limited effect. Since chronic pain is more than just physical, somatic pain that involves both affective and cognitive components, a multimodal approach is necessary to improve symptoms and reduce disability. VS/ALIC neuromodulation has been shown to improve symptoms of anxiety, treatment-resistant depression, and obsessive-compulsive disorder. Focusing on the affective aspects of chronic pain may improve sense of wellbeing and reduce anxiety related to worsening the chronic pain by performing daily activities. Despite the improvements in affective measures, no PDI change was appreciated.

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Stroke Alert

By Matthew E. Fink, MD

What Is the Risk of Hemorrhage During Pregnancy for a Woman with Brain Arteriovenous Malformation?

SOURCE: Porras JL, Yang W, Philadelphia E, et al. Hemorrhage risk of brain arteriovenous malformations during pregnancy and puerperium in a North American cohort. *Stroke* 2017;48:1507-1513. doi: 10.1161/STROKEAHA.117.016828.

The risk of hemorrhage in a pregnant woman with a brain arteriovenous malformation (AVM) is uncertain and management is controversial. Investigators at Johns Hopkins Medicine retrospectively reviewed female patients with AVMs evaluated from 1990 to 2015. They considered the exposure during pregnancy up to 40 weeks and the puerperium for six weeks postpartum, for each full-term pregnancy, and a six-week exposure for each abortion. Hemorrhage events and patient years were calculated for both the exposure as well as non-exposure, defined as either the interval from birth until AVM obliteration or until the last follow-up after subtracting the exposure. A ratio test was used to compare the rate of hemorrhage between the exposure and nonexposure periods.

Two hundred seventy patients with AVMs were included, with a mean age of 35 ± 19.6 years, with 61% white, 22% black, 3% Hispanic, 2% Asian, and 11% other ethnic groups. Nine of the female patients experienced AVM rupture during pregnancy or puerperium. Mean age at AVM rupture was 29.7 years and the mean AVM size was 3.2 cm. Overall, the annual hemorrhage rate for 149 total hemorrhages during an average of 11,097 patient years was 1.34%. There were 140 hemorrhages in nonexposed women and nine hemorrhages in pregnant women, translating to an annual hemorrhage rate of 1.3% in nonpregnant women vs. 5.7% in pregnant women ($P < 0.001$). These results remain controversial and contradict other studies recently published, and this difference may be related to the technique used for calculation as well as case ascertainment. Currently, the true risk of AVM hemorrhage during pregnancy is uncertain.

Atypical Transient Symptoms Require Aggressive Investigation for Cause

SOURCE: Lavallee PC, Sissani L, Labreuche J, et al. Clinical significance of isolated atypical transient symptoms in a cohort with transient ischemic attack. *Stroke* 2017;48:1495-1500. doi: 10.1161/STROKEAHA.117.016743.

Atypical transient symptoms, such as partial sensory deficit, dysarthria, vertigo and unsteadiness, unusual visual deficits, and diplopia, usually are not classified as transient ischemic attacks, and they frequently are not investigated in the same fashion. Investigators undertook detailed evaluation of these patients admitted to their TIA clinic from 2003 until 2008, and investigated them with systematic brain, arterial, and cardiac investigations. They compared the prevalence of recent brain infarction on imaging, as well as evidence of intracranial or extracranial atherosclerosis, cervical artery dissection, or a source of cardiac embolism. They then quantified the one-year risk of major vascular events in patients who had isolated typical or atypical transient symptoms.

Among 1,850 patients with possible ischemic diagnoses, 43% had isolated transient symptoms, with 34% being typical TIAs and 9.6% being atypical. The presence of brain infarction on imaging was similar in both groups of patients. One-year risk of recurrent major vascular events was not significantly different between patients who had typical TIA symptoms or atypical isolated or non-isolated symptoms. Therefore, these patients should be investigated intensively in a manner similar to patients with classical TIA symptoms.

Continued from page 87

Yet, five of nine patients would have the procedure again. Thus, despite the lack of improvement in disability from pain, mood improvements did show preliminary benefits in these patients. This study, though promising and adding to our understanding of chronic pain, has several limitations. The first limitation is the small sample size, followed by the relatively short follow-up, despite the 18-month extension. As we know from the literature of DBS for movement disorders, it may take longer than 18 months to demonstrate benefit, particularly in patients with longer standing disease. This is particularly true in dystonia patients with severe postures that respond after six months or longer of stimulation and continue to improve over time. The anatomical differences in stroke patients also may contribute to challenges in accurately implanting and subsequently programming these patients, which can lead to unwanted side effects from spread of stimulation to adjacent structures. Also, it still is unclear what the ideal stimulation parameters are in these affective disorders, and further DBS studies are necessary to determine them. Finally, as cognition is affected in stroke, the long-term effects of neuromodulation of the VS/ALIC on cognition would need to be assessed. The movement disorders literature regarding the effects of DBS on cognition is not consistent enough to draw conclusions. ■

CME QUESTIONS

1. **What was the primary endpoint for the trial of cannabidiol vs. placebo for drug-resistant seizures in Dravet syndrome?**
   a. Reduction in all seizure types from baseline
   b. Reduction in non-convulsive seizures from baseline
   c. 50% reduction in seizures from baseline
   d. Reduction in convulsive seizures from baseline
2. **In POEMS neuropathy, compared to MGUS neuropathy, which of following statements is true?**
   a. Reduced motor amplitudes are indicative of POEMS, rather than MGUS, neuropathy.
   b. Slow motor conduction velocities are indicative of POEMS, rather than MGUS, neuropathy.
   c. High terminal latency indices are indicative of POEMS, rather than MGUS, neuropathy.
   d. All of the above
3. **Which of the following was not a finding from the Multidomain Alzheimer Preventive Trial?**
   a. In the intention-to-treat population, there was no significant difference in three-year cognitive decline between any of the intervention groups and the placebo group.
   b. In a post hoc analysis, pooled analyses of all multidomain intervention subjects revealed less cognitive decline than for those who received conventional care.
   c. There was a significant three-year cognitive decline for participants with low baseline concentrations of docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA) in red blood cells compared to stable cognitive performances for participants with high baseline concentrations of DHA and EPA.
   d. In participants identified as amyloid-positive by PET scan, there was no significant difference in three-year cognitive decline between any of the intervention groups and the placebo group.
4. **Which structure shows a bilateral increase in mean brain perfusion (CBF) after a migraine aura?**
   a. Thalamus
   b. Frontal cortex
   c. Insular cortex
   d. Posterior cerebral cortex
   e. Calcarine cortex
5. **Which of the following statements is *false* regarding the results of the VS/ALIC neuromodulation study?**
   a. The Beck Depression Index significant improved in the "on" phase during randomization.
   b. Only three of nine participants would repeat the procedure.
   c. Affective sphere of pain parameters demonstrated improvement.
   d. Significant side effects, such as infection and wound dehiscence, resolved with treatment.

[IN FUTURE ISSUES]

Update on Neuro-Oncology