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Neurology [ALERT®]

Evidence-based summaries of the latest clinical neurology research

ABSTRACT & COMMENTARY

Clinical Features and Treatment Response in Patients with NMO Spectrum Disorders

By Jai S. Perumal, MD

Assistant Professor of Neurology, Weill Cornell Medical College

Dr. Perumal receives grant/research support from Genzyme Corp., and is on the speakers bureau for Biogen Idec, Teva Pharmaceuticals, Genzyme Corp., and Acorda Therapeutics.

SYNOPSIS: In a retrospective analysis of 871 relapses in 185 patients with neuromyelitis optica (NMO) or an NMO spectrum disorder, the authors reported that more than 80% of patients will have a partial or complete remission from their initial course of therapy.

SOURCE: Kleiter I, et al. Neuromyelitis optica: Evaluation of 871 attacks and 1153 treatment courses. *Ann Neurol* 2015; DOI: 10.1002/ana.24554.

Neuromyelitis optica (NMO) is an inflammatory disease of the central nervous system that preferentially affects the optic nerves and spinal cord. Classic NMO or Devic's disease is characterized by concurrent episodes of optic neuritis (ON) and transverse myelitis (TM). NMO spectrum disorder (NMOSD) is diagnosed in patients with isolated ON or TM who have the NMO IgG antibody, which is potentially pathogenic and has high specificity for this group of diseases. Unlike multiple sclerosis, the relapses in NMO tend to be more severe and show less recovery, often with residual deficits. Another feature of NMO that appears to be different from multiple sclerosis is that disability in NMO tends to accrue from residual deficits from relapses rather from a progressive phase. These distinguishing features make the recognition and treatment of relapses in NMO even more important.

In the present study, the authors conducted a retrospective analysis of 871 attacks in 185 patients whose data were captured in the Neuromyelits Optica Study Group (NEMOS) registry, which spans 16 tertiary referral centers and six regional hospitals in Germany. The primary objective measure was the short-term remission status post-relapse. The post-relapse remission status was categorized as complete recovery (CR) when there was full

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recovery, partial recovery (PR) when there was incomplete recovery, and no remission (NR) when there was no recovery at all.

They report the following findings:
1. **Frequency and Manifestation of Attacks:** Episodes of isolated myelitis (59.4%) were more frequent than isolated optic neuritis (28.4%), simultaneous myelitis and optic neuritis (10.2%), or other presentations. Most of the episodes of optic neuritis tended to be unilateral rather than bilateral.
2. **Remission from Attacks:** Regardless of the specific treatment modality, remission rates were significantly higher for isolated optic neuritis when compared to isolated myelitis or combined myelitis and optic neuritis.
3. **Treatment of Attacks:** High-dose intravenous steroids (HD-S) was the most commonly used treatment (70.3%) and the next was plasmapheresis/immunoadsorption (PE/IA), which was used in 19.9% of the relapses. Less commonly used treatments included IVIG, intrathecal steroids, and low-dose steroids among others.
4. **Response to Treatment:** First treatment resulted in CR in just 19.1%, PR in 64.5%, and NR in 16.4%. About a third of the attacks were treated with a second treatment course and a quarter of these were subsequently given a third course of treatment. Each escalation step significantly improved outcomes, with the second intervention having the greatest impact. PE/IA were superior to HD-S as first treatment for isolated myelitis but did not show significant difference when all attacks were pooled or in cases of optic neuritis or combined optic neuritis and myelitis.

■ COMMENTARY

The authors reported the results from their study of a large number of attacks in NMO/NMOSD patients. As has been reported previously, they demonstrated that recovery from attacks is not ideal, with myelitis and bilateral optic neuritis showing the worst outcomes. However, they show that escalation of therapy and treating patients with more than one treatment modality, especially a second treatment course, produces meaningful improvement in remission status. The limitations of this study include the retrospective nature of the analysis, potential bias that could have been introduced by factors that may have influenced the decision as to what treatment to offer to patients first, and the effect of concomitant disease-modifying therapies these patients may have been on that could have impacted severity and recovery from relapses. In conclusion, this large study corroborates findings previously reported on the severity and recovery from relapses in NMO. It demonstrates that an aggressive treatment approach utilizing more than one modality might be necessary to treat attacks in NMO. ■

ABSTRACT & COMMENTARY

Disability, Anxiety, and Depression with Medication-overuse Headache

By Louise M. Klebanoff, MD

Assistant Professor of Clinical Neurology, Weill Cornell Medical College

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

SYNOPSIS: A brief intervention that focuses on patient education can be effective in reducing headache frequency and medication dependency in patients with medication overuse headache.

SOURCE: Kristoffersen ES, et al. Disability, anxiety and depression in patients with medication-overuse headache in primary care — the BIMOH study. *Eur J Neurol* 2015;23(Suppl 1):28-35.

Medication overuse headache (MOH) affects approximately 50% of patients with chronic headaches (headaches occurring at least 15 days per month), causing significant personal burden and economic costs. The recommended treatment of MOH is withdrawal of the overused medication; however, interventions to accomplish this have varied. Education and simple advice about the relationship of medication overuse and chronic headaches may in and of itself be an effective intervention. This study examined the efficacy of this brief intervention strategy in the primary care setting.

The authors conducted a double-blind, pragmatic, cluster-randomized, controlled trial in a primary care setting in Norway from 2011-2012. They enrolled patients aged 18-50 years with self-reported chronic headaches occurring > 15 days/month and with head-ache medication use > 10 days/month. All patients met International Classifications of Headache Disorders criteria for MOH. Patients were cluster-randomized according to their general practitioners (GPs); the GPs either received training in the brief intervention prior to the study (n = 23, brief intervention [BI] group) or following completion of the study (n = 27, business as usual [BAU] group).

Patients with MOH randomized to the BI group were initially evaluated by their GP using the Severity of Dependence Scale (SDS), an easily administered five-question scale to evaluate drug dependence. Based on their SDS result, patients were given information about their SDS score and personal risk for MOH, the need to cut down on medication use, the expected gains and difficulties to be overcome, and how the withdrawal could be achieved with the GP's support. The patients discussed the need for rescue medication and/or short-term medical leave with their GP. The GPs did not prescribe medication for headache prophylaxis but left that as an option if the headaches persisted at the 3-month follow-up.

The main outcomes at 3 months were number of headache days/month, number of medication days/month, and change from baseline. Secondary outcomes were disability and psychological problems, as measured by the Migraine Disability Assessment (MIDAS), the Headache Impact Test (HIT-6), and the Hospital Anxiety and Depression Scale (HADS). The BI group had a clear reduction in both headache days and medication days when compared to the BAU group. At the 3-month follow-up, the BI group reported an average of 17.4 (13.2-21.5) headache days/month vs 24.6 (22.6-26.6) in the BAU group. The BI group reported an average of 13.4 (8.8-18.0) medication days/month vs 21.7 (19.2-24.2) in the BAU group. There was no significant difference in the MIDAS or HIT-6 scores between the two groups, although the BI group tended to have lower scores. The mean MIDAS score for all MOH patients was 70.7 (49.1-92.2) consistent with severe disability and significantly higher than patients with chronic headache (average 26.9, range 8.2-45.7) or population controls (average 7.1, range -1.1 to 15.4). There were no significant differences in the anxiety and depression scores between the BI and BAU groups; however, higher anxiety scores were noted in all MOH patients when compared to controls.

The authors concluded that for patients with MOH in a primary care setting, detoxification achieved through a behavioral, non-pharmacological intervention significantly improved headache disability without the use of prophylactic medication.

■ COMMENTARY

This small study shows that brief intervention, primarily education and physician support, can reduce headache disability in MOH patients in the primary care setting. The intervention is simple and easily administered in the office setting. Patients with MOH are among the most disabled headache patients with significant psychological comorbidity. Although headache and medication days were reduced with the intervention, after 3 months, patients continued to experience frequent headaches and psychological distress. The study supports the importance of detoxification for patients with MOH. However, additional investigation is needed to assess how to further reduce headache days and disability once the patient has completed detoxification. In addition, more aggressive interventions, such as rescue medications, corticosteroids, or early introduction of prophylactic medication need to be evaluated in future studies. ■

ABSTRACT & COMMENTARY

Simvastatin and Vitamin D for Migraine Prevention

By Dara Jamieson, MD

Associate Professor of Clinical Neurology, Weill Cornell Medical College

Dr. Jamieson reports she is a consultant for Bayer and Boehringer-Ingelheim.

SYNOPSIS: In a randomized, double-blind, placebo-controlled trial of 57 adults with episodic migraine, simvastatin plus vitamin D was effective in the prevention of headache in adults with episodic migraine.

SOURCE: Buettner C, et al. Simvastatin and vitamin D for migraine prevention: A randomized, controlled trial. *Ann Neurol* 2015; Sep 29. DOI: 10.1002/ana.24534 [Epub ahead of print].

Despite somewhat effective acute migraine headache treatments, there continues to be a need for further treatments to prevent episodic migraine. Buettner et al performed a randomized, double-blind, placebo-

controlled trial to assess the efficacy and tolerability of the twice-daily combination of simvastatin and vitamin D for migraine prevention in 57 adults with episodic migraine. Adults, recruited from the greater Boston area, had to have episodic migraine headaches, as diagnosed by the International Headache Society (ICHD-II) criteria for ≥ 3 years, with ≥ 4 headache days a month. Patients were not eligible if they had chronic migraine with ≥ 15 days of headache a month for 3 months. The majority had used multiple acute pain medications for abortive therapy. Approximately half had tried or were currently using a migraine-preventive medication. After a 12-week baseline data-gathering period, the migraineurs were randomly assigned to simvastatin 20 mg tablets twice daily plus vitamin D3 1000 IU capsules twice daily or to matching placebos for a 24-week intervention period. Headache characteristics were tracked by diary.

Compared to the placebo group, the active treatment group had statistically significantly older age, larger body mass index, and more headache days in the past 3 months (25.5 vs 18.0). Episodic migraineurs randomized to simvastatin plus vitamin D3 demonstrated a greater decrease in number of migraine days from the baseline period to intervention weeks 1 to 12 — a change of -8.0 days in the active treatment group vs +1.0 days in the placebo group ($P < 0.001$). In the second half of the treatment period, intervention weeks 13 to 24, there was a change of -9.0 days in the active group vs +3.0 days in the placebo group ($P < 0.001$). In the simvastatin plus vitamin D3 group, eight out of 28 migraineurs experienced a 50% reduction in the number of migraine days at 12 weeks, and nine out of 24 participants had the reduction at 24 weeks post-randomization. Only 1 out of 29 patients in the placebo group had a 50% reduction in the number of migraine days.

Adverse events were similar in both groups, treatment discontinuation rates were low, and blinding was successful. Creatine kinase levels were monitored with a significant elevation in one placebo group participant who was exercising vigorously and taking vitamin supplements. The results of this small preliminary study indicate that simvastatin plus vitamin D may be effective for prevention of headache in adults with episodic migraine. The authors speculated that because statins are believed to correct endothelial dysfunction, this economical approach may also reduce the risk for vascular diseases among migraineurs.

■ COMMENTARY

The authors noted that migraine is a neurological disorder associated with increased cerebrovascular and cardiovascular risk, not adequately explained, but with likely involvement of changes in the endothelial morphology. Statins have anti-inflammatory, antithrombotic, and antiplatelet properties that are independent of their more well-known lipid-lowering effect. Statins appear to stabilize the endothelium, accounting for their use in vascular risk reduction. The authors previously observed an association with statin use, with potential migraine benefit in those with higher vitamin D levels, and they postulate favorable synergism between vitamin D and statins. While these results show headache prevention with two relatively well-tolerated drugs in patients with episodic migraine, the real test of this treatment is in patients with chronic migraine. Patients who respond favorably to acute treatment with a triptan several times a month usually do not generally need to take a daily preventive medication for functional improvement. Statins are generally well tolerated, with muscle complaints noted in a small number of patients. This pilot study continues to explore that observation. But a larger study with a more diverse and better matched patient population is needed to confirm these promising results.

Migraine preventive treatment is essentially empiric, based on epidemiologic data rather than on cogent mechanistic explanation. The explanations offered to patients asking how these medications work are frustratingly vague. Any offerings on mechanisms for simvastatin and/or vitamin D are conjecture. Which of these two active treatments confers benefit is not known and the appropriate patient profile for their use is also unspecified. Low vitamin D levels are common in the United States, especially in northern climates, with lack of sun exposure in colder months. The participants' vitamin D levels were not noted in the results to see if there was a correlation with treatment response. As the individual patient profile often dictates the choice of migraine preventive medication, if migraine patients are known to have untreated elevation of LDL, encouraging treatment with simvastatin plus vitamin D makes sense. The benefit of simvastatin is likely a class effect rather than a specific agent effect, so other statins may also be efficacious.

As a coda, two of the authors and Beth Israel Deaconess Medical Center have applied for a patent for the combination of a statin and vitamin D as a prophylactic treatment for migraine. This patent application is reminiscent of the past patenting of the combination of a triptan and a nonsteroidal anti-inflammatory agent for the acute treatment of migraine, with a branded single pill combination treatment eventually coming to market after the patent expiration on Imitrex. If the combination of simvastatin and vitamin D continues to show benefit, will Zocor be rebranded with an over-the-counter vitamin? However, the generic two-pill combination may be just as efficacious, as this study was performed with generic simvastatin and vitamin D from Trader Joe's. ■

ABSTRACT & COMMENTARY

Acetylcholine Receptor Antibody Testing in Ocular 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: More than two-thirds of patients with ocular myasthenia will have a positive antibody test, and a high level may predict progression to generalized disease.

SOURCE: Peeler CE, et al. Clinical utility of acetylcholine receptor antibody testing in ocular myasthenia gravis. *JAMA Neurol* 2015;72:1170-1174.

Among patients with generalized myasthenia gravis (GMG), 80-90% have antibodies against the acetylcholine receptor (AchR Ab), 5-8% have antibodies against muscle-specific kinase (MuSK), and the remainder are "seronegative." Among patients with ocular myasthenia gravis, AchR Ab seropositivity is approximately 50%, with a few case reports of MuSK Ab positivity, and even fewer with positive LRP4 (low-density lipoprotein receptor-related protein 4) antibodies. Are these results accurate, and do they correlate with progression to generalized myasthenia?

Following institutional review board approval, a retrospective observational cohort study was performed on 223 ocular myasthenia gravis patients seen by the Neuro-Ophthalmology Service, Massachusetts Eye and Ear Infirmary, and the Department of Ophthalmology and Visual Sciences, University of Michigan, Ann Arbor, between July 1986 and May 2013. Data extracted included gender, age at symptom onset, ocular symptoms of ptosis and/or diplopia, duration of follow-up, and, if relevant, time to progression to GMG. AchR binding antibody testing was performed on all, with values > 0.02 nmol/L considered positive. Statistical analysis included two-sample *t* tests, multiple logistic regression, Kaplan-Meier estimates, and log-rank tests.

Of 223 ocular myasthenia patients, 62.3% (n = 139) and 37.7% (n = 84) were male and female, respectively, with a mean age at diagnosis of 59.2 years. Ptosis or diplopia alone were seen in 11.2% and 34.1%, respectively, with 54.7% having both ptosis and diplopia. AchR binding antibody was positive in 70.9% (n = 158), more frequent in men than women, with a mean level of 6.13 nmol/L. Progression to GMG occurred in 20.2% during a mean follow-up of 5 years. Older age at diagnosis (61.1 years vs 54.7 years in seronegative patients) and progression to GMG were significantly associated with seropositivity, and progression to GMG correlated with significantly higher antibody levels, 12.7 nmol/L compared to 4.2 nmol/L, in those who did not generalize. This is the first report to note an association between elevated AchR antibody levels and progression from ocular to generalized myasthenia.

■ COMMENTARY

What is safe, effective, and tolerable therapy for ocular myasthenia gravis? EPITOME (Effectiveness of Prednisone for the Treatment of Ocular Myasthenia) recently addressed this question in a superbly designed, double-blind, randomized, parallel-group, controlled trial among six academic centers across Canada and the United States.

Unfortunately, after 34 months, a mere 11 patients were randomized, with only nine completing the 16 weeks of therapy. Among 145 patients asked to participate, 107 failed prescreening and 23 declined. Of the remaining 15 OMG patients of new or recent onset who failed pyridostigmine and had not previously received immunosuppressive or immunomodulating therapy, 11 were randomized to receive either placebo or prednisone 10 mg daily, increased to a maximum of 40 mg/day over 16 weeks. Prednisone resulted in improvement over a median of 14 weeks, at an average dose of 15 mg/day, with infrequent and mild adverse effects.[1]

It is disappointing that so little return was achieved for such a herculean effort. Indeed, there are more authors on this paper than participants in the study. Thus, one wonders why a letter to the editor would not have sufficed to disseminate this small study. ■

REFERENCE

1. Benetar M, et al. Efficacy of prednisone for the treatment of ocular myasthenia (EPITOME): A randomized controlled trial. *Muscle Nerve* 2015; July 14. doi: 10.1002/mus.24769 [Epub ahead of print].

ABSTRACT & COMMENTARY

Vision Problems After Ischemic Stroke: Effects on Quality of Life

By Marc Dinkin, MD

Assistant Professor of Ophthalmology, Weill Cornell Medical College

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

SYNOPSIS: Visual impairments are common in stroke survivors and should prompt a careful ophthalmologic evaluation, since many of the problems are ocular and not neurological.

SOURCE: Sand KM, et al. Vision problems in ischaemic stroke patients: Effects on life quality and disability. *Eur J Neurol* 2015; 23(Suppl 1):1-7.

All too often, the visual deficits of acute stroke victims remain under-recognized, overshadowed by the more obvious motor and language manifestations observed at presentation. A visual field defect, for example, has to be searched for with careful confrontational visual fields, and in some cases of stroke-related diplopia, the ocular misalignment is subtle enough to escape detection by testing of ocular motility in the absence of cross-cover testing. Even when these visual deficits are recognized, they may be de-emphasized, while initial rehabilitation strategies focus on the important task of recovering mobility and speech. Ultimately, problems with vision can have a profound effect on stroke patients' quality of life, with an increase in the risk of depression, institutionalization, and mortality. With this in mind, Sand and colleagues undertook one of the first studies to examine the long-term afferent and efferent visual outcomes in stroke patients, and their effects on quality of life.

The authors approached the question by mailing a questionnaire to all 6-month survivors of ischemic stroke who were seen at the Haukeland University Hospital in Bergen, Norway, between 2006 and 2008. The questionnaire included self-assessments of health, fatigue, mood, and pain severity, including the 15D, Euro-Qol 5D, Hospital Anxiety Depression Scale (HADS), fatigue severity scale (FSS), and Barthel Index (BI). Assessment of vision specifically was based on responses to the second question on the 15D battery, which asked patients to rate their visual abilities ranging from a score of 1 (no difficulty watching television or reading newspapers) to 5 (needs help to walk around; almost blind).

Of the 328 patients with cerebral infarction who responded, at a mean of 372 days after the stroke, 25.4% self-reported a visual problem, with 6.5% reporting either great difficulty watching television and reading, not able to watch TV or read, or not able to walk independently. Those who did report a vision problem were older, more likely to be unemployed, and more likely to have a prior infarct or prior depression. Their baseline NIHSS was higher and, not surprisingly, the sub-scores for eye movements and visual fields were higher. The study's primary finding was that the presence of visual problems was associated with a worse self-reported sense of general health, more pain and headache, lower quality of life scores, more depression, and a smaller chance of being independent. Having vision problems was also independently associated with more difficulty with feeding, transfers, grooming, toilet use, bathing, mobility, climbing stairs, dressing, and using the bathroom.

The study concluded with an algorithm for visual rehabilitation including technical aids and structured visual stimulation and exercises aimed at normalizing fixation; saccades; visual attention; visuospatial orientation, accommodation, convergence; visual search; and binocular vision.

■ COMMENTARY

This study serves as a strong reminder of the relatively high prevalence of visual problems in the post-stroke population, and perhaps more importantly, of the profound effect that even mild-to-moderate visual dysfunction can have on these patients' quality of life. It is notable that the overall EQ-5D utility score showed a fair correspondence with self-reported vision status on the 15D, underlining how crucial good vision is to patients' daily functioning.

The authors did not evaluate the precise visual problems or even differentiate afferent from efferent dysfunction, and it is therefore likely that many of the visual problems in this population were not stroke-related. Patients with baseline glaucoma, macular degeneration, diabetic or hypertensive retinopathy, or ischemic optic neuropathy were not excluded from the study and are all more common in older patients, so it is important to understand that this paper does not describe *stroke-related visual problems*, but instead vision problems after stroke. Fu-

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Stroke Alert

By Matthew E. Fink, MD

Left Atrial Dysfunction Without Fibrillation Increases Stroke Risk

SOURCE: Kamel H, et al. Electrocardiographic left atrial abnormality and stroke subtype in the Atherosclerosis Risk in Communities Study. *Ann Neurol* 2015;78:670-678.

Atrial fibrillation is a known risk factor for ischemic stroke, with a three- to five-fold heightened risk. However, it is now being recognized that left atrial abnormalities that do not necessarily result in atrial fibrillation, such as endothelial dysfunction, fibrosis, and chamber dilatation, may also increase the risk of stroke. All of these abnormalities may increase the risk of thrombus formation in the left atrium and subsequent cerebral embolism. In this study, the investigators analyzed the presence of left atrial abnormality as defined on electrocardiogram by the P-wave terminal force in lead V1 > 4000 μV per meter-squared. The cohort consisted of 14,542 participants aged 45 to 64 years, prospectively enrolled in a population-based study, and free of clinically apparent atrial fibrillation. Outcomes were ischemic stroke, divided into non-lacunar and lacunar stroke. During a median follow-up period of 22 years, 904 participants (6.2%) experienced a definite or probable ischemic stroke. The incidence of stroke was higher in those with a baseline left atrial abnormality as defined above, 6.3 per 1000 patient-years, compared to 2.9 per 1000 patient-years in those without atrial abnormalities. In a regression model, the presence of a left atrial abnormality was associated with a hazard ratio of 1.33 (statistically significant). This association was limited to non-lacunar stroke (hazard ratio = 1.49) and would be consistent with cardiogenic embolism as a cause for ischemic stroke. Left atrial abnormalities should be investigated and searched for in patients with ischemic stroke consistent with cardiogenic embolism, even in the absence of atrial fibrillation. ■

Loss of Consciousness at Onset of Aneurysmal SAH: Poor Prognosis

SOURCE: Suwatcharangkoon S, et al. Loss of consciousness at onset of subarachnoid hemorrhage as an important marker of early brain injury *JAMA Neurol* 2015; Nov. 9. doi:10.1001/jamaneurol.2015.3188 [Epub ahead of print].

Aneurysmal subarachnoid hemorrhage (SAH) is one of the few acute neurological disorders that may present with out-of-hospital respiratory and cardiac arrest, in the setting of loss of consciousness. The authors did a retrospective analysis of 1460 consecutively treated patients at a large urban academic medical center to identify those patients who had loss of consciousness at onset of hemorrhage and assessed their treatment and prognosis. Outcome was measured using the modified Rankin scale score, 12 months after onset of illness. In the study, 590 patients (40.4%) reported loss of consciousness at the onset of SAH, and this was associated with poor clinical grade on admission, more subarachnoid and intraventricular blood seen on CT scan, and a higher frequency of generalized cerebral edema. These patients also had more episodes of seizure-like activity, and about 10% presented with cardiopulmonary arrest compared to < 1% of patients who did not experience loss of consciousness. Death or severe disability at 12 months was independently associated with loss of consciousness, after adjustment for other risk factors, with an adjusted odds ratio of 1.94 compared to those without loss of consciousness. During the hospital course, loss of consciousness at onset was not associated with rebleeding of the aneurysm or delayed cerebral ischemia. Loss of consciousness at onset of SAH is an indicator of early brain injury and predicts poor functional outcome or death at 12 months. ■

Small Vessel Disease Often Accompanies Large Vessel Intracranial Atherosclerosis

SOURCE: Kwon HM, et al. Frequency, risk factors, and outcome of coexistent small vessel disease and intracranial arterial stenosis: Results from the Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) Trial. *JAMA Neurol* 2015; Nov 30. doi:10.1001/jamaneurol.2015.3145 [Epub ahead of print].

The SAMMPRIS trial investigated the consequences of medical vs endovascular therapy for the treatment of symptomatic intracranial atherosclerosis, but the trial was terminated early because of the high rate of complications in the endovascular arm. The medical arm included intensive medical therapy with lifestyle modifications, use of statins, and dual antiplatelet therapy, and this resulted in an unexpected low rate of recurrent stroke in the medical arm. The investigators then performed a post-hoc analysis of 451 participants to ascertain the prevalence and associated risk factors of small vessel disease as it relates to known intracranial atherosclerosis of large vessels. A total of 313 participants had baseline brain MRI imaging and, of those, 49.5% had small vessel disease based on the presence of lacunar infarction, high-grade white matter hyperintensities, or microbleeds. Variables that were significantly more prevalent in the small vessel disease group, compared to the others, were advanced age, higher systolic blood pressure, higher glucose level, and lower Montréal Cognitive Assessment score. Additional significant variables were the number of patients with diabetes mellitus, coronary artery disease, or stroke before the qualifying event. Although there was an association between the presence of small vessel disease and any ischemic stroke, small vessel disease was not associated with an increased risk of stroke in the territory of the affected atherosclerotic large vessel. This study points out the high prevalence of coexisting small vessel disease with large vessel atherosclerosis, but it did not clarify any of the mechanisms or etiologies for small vessel disease, which are many and varied. ■

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ture surveys might offer more specific insights by eliciting problems with monocular vision loss, homonymous visual field loss, horizontal and vertical diplopia and oscillopsia, and asking patients to identify whether the problems began with their stroke or were unrelated. Furthermore, while the study reported higher rates of depression and fatigue in patients with greater visual problems, the cause and effect relationship is unclear. For example, a patient with depression might self-report greater difficulties from a right homonymous hemianopia as compared to a non-depressed patient with the same field defect. The authors pointed out a novel finding of the association between visual problems and fatigue, but here also, background fatigue might enhance one's sense of visual difficulty. Despite these limitations, this study presents a powerful argument for greater attention paid to the visual consequences of stroke, and toward attempts at maximizing compensation and function through focused vision rehabilitation. ■

CME QUESTIONS

1. **Which of the following statements about treatment of neuromyelitis optica spectrum disorders is true?**
   a. Patients with acute relapse usually have a complete remission when treated with high-dose intravenous steroids.
   b. Patients with acute relapse usually have a complete remission when treated with plasmapheresis.
   c. The highest rate of remission from relapse occurs in patients with unilateral optic neuritis.
   d. Successful treatment of a relapse will prevent future relapses.
2. **For patients with medication overuse headache, which of the following interventions has been shown to be effective in reducing headache days and disability?**
   a. A brief course of opioid analgesics
   b. A brief course of corticosteroids
   c. Introduction of medication for headache prophylaxis
   d. Education regarding the relationship between medication use and chronic headache
3. **Which of the following statements about the combination of simvastatin and vitamin D for migraine prevention is true?**
   a. A statistically significant 50% reduction in the number of headache days was seen in the treatment group.
   b. Despite efficacy, the active treatment combination was poorly tolerated.
   c. A significant elevation of CK associated with statin treatment was seen in one migraineur.
   d. Benefit was correlated with baseline low vitamin D levels.
4. **Which of the following statements is true?**
   a. Elevated levels of serum acetylcholine receptor (AchR) binding antibody are found in approximately 35% of patients with ocular myasthenia
   b. Progression to generalized myasthenia does not occur in ocular myasthenia
   c. Progression to generalized myasthenia occurs in 50% of ocular myasthenia
   d. Patients who are older at diagnosis of ocular myasthenia are more likely to progress to generalized myasthenia than those who are younger
5. **More than half of ischemic stroke survivors report a severe visual impairment 6 months after the stroke occurred.**
   a. True
   b. False
6. **Atrial fibrillation is the only significant cause for cardiogenic cerebral embolism.**
   a. True
   b. False
7. **Loss of consciousness at onset of aneurysmal subarachnoid hemorrhage indicates early brain injury.**
   a. True
   b. False
8. **Large vessel atherosclerotic disease of intracranial arteries is often accompanied by small vessel disease and lacunar strokes.**
   a. True
   b. False

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