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[ALERT®]

Evidence-based summaries of the latest clinical neurology research

ABSTRACT & COMMENTARY

Autoimmune Encephalitis: Not Rare and Increasing

By Silky Pahlajani, MD

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

SYNOPSIS: Detection of autoimmune encephalitis is increasing over time. According to the results from this population-based study, its prevalence and incidence are comparable to infectious encephalitis.

SOURCE: Dubey D, Pittock SJ, Kelly CR, et al. Autoimmune encephalitis epidemiology and comparison to infectious encephalitis. *Ann Neurol* 2018;83:166-177.

The traditional diagnostic approach to encephalitis, a broad term for brain inflammation, has focused primarily on infectious causes. Recent discovery of various neuronal antibodies and associated forms of autoimmune encephalitis has led to a paradigm shift. Despite increasing recognition and diagnosis of autoimmune encephalitis, studies pertaining to epidemiology are scant.

The authors of this population-based, comparative study compared the prevalence and incidence of autoimmune encephalitis and infectious encephalitis in residents of Olmsted County, MN. The analysis includes patients of all ages, both sexes, and ethnic minorities. Search of medical records from Jan. 1, 1995, to Dec. 31, 2015, selected all patients with encephalitis and other potentially relevant diagnostic codes. Of the 570 patients identified, 57 met inclusion criteria, 28 for autoimmune encephalitis (definite or probable) and 29 for infectious encephalitis. Diagnosis of definite or probable autoimmune encephalitis was determined by the 2016 diagnostic criteria published by Graus et al.[1] The comparison group with infectious encephalitis included meningoencephalitis and progressive multifocal leukoencephalopathy (PML) but required confirmation of an infectious pathogen (bacterial, viral, fungal, or parasitic). Patients with encephalitis were excluded if the final diagnosis was possible autoimmune encephalitis not meeting criteria for definite or probable, presumed infectious encephalitis without a confirmed pathogen, a

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prion disorder, and encephalitis of unknown etiology or immune-related disorder.

Results of statistical analysis and age- and sex-adjusted calculations revealed a prevalence of 13.7 per 100,000 and incidence of 0.8 for autoimmune encephalitis, comparable to that of infectious encephalitis with a prevalence of 11.6 per 100,000 and incidence of 1.0. Additionally, the authors included two tables that compared rates of occurrence for each subtype. The prevalence of autoimmune encephalitis was almost three times higher in African-Americans than Caucasians (38.3 per 100,000 and 13.7 per 100,000, respectively), and incidence was four times higher in African-Americans than Caucasians (2.8 per 100,000 person-years vs. 0.7 per 100,000 person-years, respectively). No differences were found in ethnic proportionality pertaining to prevalence or incidence of infectious encephalitis. Over two decades, the incidence of autoimmune encephalitis tripled from 0.4 between 1995-2005 to 1.2 between 2006-2015, mainly because of increased detection of neural-specific IgG-associated encephalitis. In comparison, incidence of infectious encephalitis remained unchanged (1.0) during both time intervals. In addition to increased detection of autoimmune encephalitis, there is also a greater tendency to relapse, therefore increasing disease burden.

■ COMMENTARY

This is the first population-based study to analyze the prevalence and incidence of autoimmune encephalitis, two of the most fundamental measures in epidemiology. Many clinicians still consider autoimmune encephalitis to be a "diagnosis of exclusion" or "rare" when compared to infectious encephalitis. Results of this study contradict that presumption and serve as an eye-opener. Knowing the epidemiology of autoimmune encephalitis is crucial; it provides context for diagnostic decision-making and allows for appropriate allocation of resources and healthcare planning. A practical example of this is demonstrated by the fact that immunoglobulin (IVIG), commonly used for acute and maintenance treatment of autoimmune encephalitis, is not covered by most insurance companies and is considered experimental. The cost of IVIG is in tens of thousands of dollars. Patients who are unable to afford treatment and therefore are left untreated perpetuate the existing severe disease burden from encephalitis. A few limitations of this study include small sample size, lack of a population-based study for direct comparison, and variations in diagnostic criteria for autoimmune vs. infectious encephalitis. Nonetheless, this study is a great starting point and demonstrates the importance of epidemiological data as well as the need for more studies to assess frequency and occurrence rate of autoimmune encephalitis in other populations. ■

REFERENCE

1. Graus F, Titulaer MJ, Balu R, et al. A clinical approach to diagnosis of autoimmune encephalitis. *Lancet Neurol* 2016;15:391-404.

ABSTRACT & COMMENTARY

Coprescription of Triptans and SSRI-type Medications and the Serotonin Syndrome

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 recent study provided reassurance that the use of triptan antimigraine medications with selective serotonin reuptake inhibitor and selective norepinephrine reuptake inhibitor antidepressants is safe.

SOURCE: Orlova Y, Rizzoli P, Loder E. Association of coprescription of triptan antimigraine drugs and selective serotonin reuptake inhibitor or selective norepinephrine reuptake inhibitor antidepressants with serotonin syndrome. *JAMA Neurol* 2018 Feb. 26. doi:10.1001/jamaneurol.2017.S144. [Epub ahead of print].

Depression and migraine are highly prevalent, chronic disorders that occur together more often than would be expected by chance. Selective serotonin reuptake inhibitors (SSRIs) and selective norepinephrine reuptake inhibitors (SNRIs) commonly are used to treat depression. Triptan antimigraine drugs commonly are prescribed to treat migraines. Evidence has suggested that between 20-25% of triptan users also are prescribed SSRI or SNRI antidepressants. There have been several case reports of serotonin syndrome in patients coprescribed these medications.

Serotonin syndrome is thought to result from elevated serotonin levels. Patients present with variable symptoms, including tachycardia, unstable blood pressure, hyperthermia, nausea, vomiting, and diarrhea. Although the severity is variable, the condition can be fatal. In 2006, the FDA issued an advisory about the risk of serotonin syndrome associated with concomitant use of triptan antimigraine medications with SSRIs and SNRIs. Following the FDA advisory, pharmacy systems and other decision support systems started issuing safety alerts when coprescription occurs. These alerts can disrupt clinical care. Neurologists treating migraine infrequently have seen serotonin syndrome in clinical practice. A position paper by the American Headache Society questioned the validity of the FDA advisory.

The authors conducted a study to identify patients who were coprescribed triptans and SSRIs/SNRIs to assess the risk of serotonin syndrome. They used the Partners Research Data Registry to identify patients who had been coprescribed triptans and SSRIs/SNRIs from Jan. 1, 2001, through Dec. 31, 2014. Investigators searched the records for serotonin syndrome and other extrapyramidal diseases and abnormal movement disorders, and then one investigator reviewed the results to assess if the patients met diagnostic criteria (either Sternbach criteria or Hunter criteria) for serotonin syndrome. The overall incidence rate for serotonin syndrome was determined by dividing the number cases by the person-years at risk during the study period.

The authors identified 47,968 patients who were prescribed triptans during the 14-year study period, with 19,017 patients also prescribed an SSRI or SNRI. Of these 19,017 patients, 229 (0.01%) had a diagnosis of extrapyramidal syndrome at some point in time, with serotonin syndrome clinically suspected in 17 patients. In only two cases, triptans were used in close temporal relation to the development of symptoms; in both cases, symptoms actually started prior to ingesting the triptan. Only seven cases occurred during a year in which coprescription of triptans and an SSRI or SNRI was documented in the medical record. In more than 30,000 patient-years of exposure, there were no life-threatening cases of serotonin syndrome and no cases in which triptan use was unequivocally implicated as a cause. The estimates suggest that the incidence of serotonin syndrome in patients coprescribed triptans and SSRIs or SNRIs ranged from zero to four cases per 10,000 person-years of exposure.

■ COMMENTARY

Serotonin syndrome is rare in patients who are coprescribed SSRI or SNRI antidepressants and triptan antimigraine medications. From a biological perspective, it is uncertain how triptans, which are serotonin agonists with high affinity for serotonin 1B and 1D receptors, could cause serotonin syndrome, which is thought to be mediated by serotonin 2A receptors. This study provides additional reassurance regarding the safe use of triptan antimigraine medications with SSRI and SNRI antidepressants. ■

ABSTRACT & COMMENTARY

Postpartum Headache May Be a Symptom of a Serious Problem

By Dara G. Jamieson, MD

Associate Professor of Clinical Neurology, Weill Cornell Medical College

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

SYNOPSIS: Consultation for acute postpartum headache resulted in the diagnosis of a secondary cause of headache in almost three out of four women, with almost half of the secondary headaches due to a hypertensive disorder of pregnancy or to cerebrovascular disease.

SOURCE: Vgontzas A, Robbins MS. A hospital-based retrospective study of acute postpartum headache *Headache* 2018 Feb. 15; doi: 10.1111/head.13279. [Epub ahead of print].

In the postpartum period, changes in hormones, blood volume, and spinal fluid dynamics can precipitate headache. Vgontzas et al reviewed the causes of acute headache in postpartum women, with the goal of distinguishing between primary and secondary headache types. The retrospective study of consecutive postpartum (up to six weeks after delivery) women 18 years of age and older who received a neurological consultation requested by

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the obstetrical service or the emergency department for headache was undertaken at a large urban tertiary-care hospital (Montefiore Medical Center, Bronx) between July 1, 2009, and Dec. 31, 2016. Demographic and obstetrical data were gleaned from chart review. Headaches were diagnosed according to the International Headache Society classification criteria and were segregated into primary and secondary headache groups. The 63 women with postpartum headache had a mean age of 29.5 years. One-third of the women were Hispanic, 30% were Black/African-American, 9.5% were white/Caucasian, and 3.2% were Asian. Overall, 54% of the women had a past headache history.

Of the 63 women who presented with acute postpartum headache, 17 (27.0%) were diagnosed with a primary headache disorder and 46 (73.0%) were diagnosed with a secondary headache disorder. A prior history of headaches was noted in more women in the primary headache group compared to in the secondary headache group (76.4 vs. 45.7; $P = 0.045$), but no patient characteristics were significantly different between the two headache groups. The headaches occurred 4.7 ± 7.3 days postpartum. Migraine was the predominant primary headache type (76.5%). Tension-type headache, occipital neuralgia, cervicogenic headache, and primary thunderclap headache (with a history of migraine and negative evaluation) each were diagnosed in four patients. Secondary headache types were postdural puncture headache (PDPH; 45.7%), uncomplicated postpartum preeclampsia (26.1%), and a diverse group of cerebrovascular headache disorders (21.7%), including pituitary apoplexy, cerebral venous thrombosis, Moyamoya, reversible cerebral vasoconstriction syndrome, posterior reversible encephalopathy syndrome, and vertebral artery dissection. Patients with PDPH presented within 24 hours of delivery with diffuse head localization of the pain. Significant factors associated with having a secondary headache included a lack of a prior headache history (54.3% vs. 23.6%), an orthostatic pattern of the pain (43.5% vs. 5.9%), and abnormal brain imaging (40.5% vs. 0%).

The authors noted that for consultations in their institution, secondary headache comprised almost 75% of all acute headache diagnoses during the postpartum period, compared to only 35% of diagnoses of secondary headache occurring during pregnancy itself. The most common secondary headache disorder diagnosed was PDPH; however, headaches attributable to pre-eclampsia or cerebrovascular disorders comprised half of all secondary headaches occurring in the six-week period after delivery. The patients whose headache developed more than 24 hours after delivery were more likely to have a migraine or a non-PDPH secondary headache type. The high rate of secondary headaches in this review may reflect the sample for whom urgent neurology consultation was requested. Vgontzas et al noted that prior prospective studies of headache in postpartum women overall have reported very low rates of secondary headache. They concluded that if the acute postpartum headache does not fit the criteria for PDPH, then neuroimaging, as well as monitoring for acute hypertensive disorders of pregnancy, is indicated.

■ COMMENTARY

In this review of 7.5 years of urgent consultation for acute postpartum headache, a secondary cause of the headache was found in almost three out of four women. Since a secondary cause of headache generally dictates some specific intervention, this differentiation is crucial. The high percentage of secondary postpartum headaches in this recent time frame in the authors' institution may reflect the presence of risk factors for some vascular disorders of pregnancy, including increased maternal age and Black/African-American ethnicity, as well as the prevalence of epidural/spinal anesthesia for delivery.

The most common secondary headache, PDPH, has characteristics of timing (hours after the dural puncture) and exacerbation (worse with change in position between upright and standing) that can indicate the diagnosis even without brain imaging. Generally, the headache with PDPH is self-limited, and women usually need only reassurance, hydration, and possibly a blood patch before the headache dissipates. However, the diagnosis and treatment of hypertensive disorders of pregnancy such as pre-eclampsia, eclampsia, and HELLP (Hemolysis, Elevated Liver enzymes, Low Platelet count) syndrome, which often are heralded by a headache, is critical to prevent the rare but devastating complications of intraparenchymal hemorrhage and ischemic stroke. A prior history of migraine headaches should not diminish the concern about a headache due to hypertensive disorders of pregnancy, as a migraine history is a risk factor. Other cerebrovascular disorders seen in the peripartum period also may need immediate diagnosis and specific treatment, such as anticoagulation for cerebral venous thrombosis. This high secondary headache risk emphasizes the importance of a detailed headache history and brain imaging when consulted for an acute postpartum headache. If a woman in the postpartum period has an acute headache that does not fit easily into a primary headache or PDPH category, then an MRI of the brain should be obtained and her blood pressure should be closely monitored and treated appropriately. ■

ABSTRACT & COMMENTARY

Lessons Learned From a Failed Anti-amyloid Trial for Alzheimer's Disease

By Makoto Ishii, MD, PhD

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

SYNOPSIS: Despite the disappointing results in EXPEDITION 3, modifications of clinical trials for Alzheimer's disease (AD) should be undertaken and trials targeting preclinical or early AD should continue with anti-amyloid agents.

SOURCE: Honig LS, Vellas B, Woodward M, et al. Trial of solanezumab for mild dementia due to Alzheimer's disease. *N Engl J Med* 2018;378:321-330.

Alzheimer's disease (AD) remains an incurable dementia without any disease-modifying therapy and no new FDA-approved drug since memantine in 2003. EXPEDITION 3 is the third Phase III clinical trial using solanezumab, a humanized monoclonal antibody designed to increase clearance from the brain of soluble amyloid-beta. Soluble amyloid-beta was targeted, as it was believed to be the most toxic form of amyloid-beta leading to synaptic dysfunction and preceding the deposition of insoluble fibrillary amyloid. In the earlier Phase III trials, EXPEDITION 1 and 2, solanezumab did not lead to significant reduction in the decline in cognition or function in those with mild-to-moderate AD. However, prespecified secondary analyses found that mild AD subjects receiving solanezumab had 34% less cognitive decline and 18% less functional decline compared to those receiving placebo. Therefore, EXPEDITION 3 was conducted to investigate the effects of solanezumab, specifically in mild AD.

EXPEDITION3 was designed as a double-blind, placebo-controlled, Phase III trial in mild AD, defined as Mini-Mental State Examination (MMSE) score of 20 to 26. Male and female subjects from 55 to 90 years of age who met the clinical diagnostic criteria and had biomarker evidence of cerebral amyloid-beta deposition by either cerebrospinal fluid (CSF) or florbetapir PET scans were enrolled in the study. Subjects received intravenous infusions of either 400 mg of solanezumab or placebo every four weeks for 76 weeks, with an optional 24-month, open-label period after completion of the double-blind period. Concomitant drug therapy with acetylcholinesterase inhibitors and memantine was allowed.

Between 2013 and 2016, 2,129 subjects underwent randomization, with 1,822 (85%) subjects completing the trial in equal numbers between the solanezumab and placebo groups. The primary outcome measure of change from baseline to week 80 on the 14-item cognitive subscale of the Alzheimer's Disease Assessment Scale (ADAS-Cog14) was not statistically different between the groups (change, 6.65 in solanezumab group and 7.44 in placebo group; difference, -0.80; $P = 0.10$). Because of the failure regarding the primary outcome, secondary outcomes, which included additional cognitive and functional scores such as the MMSE and Clinical Dementia Rating Scale-Sum of Boxes, were reported in descriptive fashion. Overall, there appears to be a trend in the secondary outcome measures toward modest benefit in the solanezumab compared to the placebo groups. Although detailed analyses of biomarkers were not provided, compared to placebo group, the solanezumab group had increased plasma and CSF levels of total amyloid-beta(1-40) and (1-42) levels, decreased CSF-free amyloid-beta(1-42) levels, and unchanged CSF-free amyloid-beta(1-40) levels. Amyloid deposition by florbetapir PET, tau pathology by CSF and flortaucipir PET, and MRI measures of whole brain or ventricular size were not different between the groups.

Adverse events were similar between the groups, with approximately 4% in each group discontinuing the trial because of an adverse event. Presence of antidrug and neutralizing antibodies, an important consideration in immunotherapy trials, similarly was low in both groups after exposure to the study drug. Amyloid-related abnormality of edema or effusions was seen in one case in the solanezumab group and two cases in the placebo group, which all were asymptomatic.

■ COMMENTARY

The disappointing results from EXPEDITION 3 undoubtedly led to gloomy headlines about another failed AD trial and provided further fuel to critics of the amyloid hypothesis. Failures from earlier trials could be attributed to the inclusion of non-AD dementia subjects, which was as high as 25% in the EXPEDITION 1 and 2 trials, and the lack of drug efficacy, once significant neurodegeneration occurs, as with moderate AD. However, both possibilities were taken into account for

EXPEDITION 3 and the results were negative. Does this mean that amyloid-beta was the wrong target and the amyloid hypothesis was disproved?

EXPEDITION 3 does not prove or disprove amyloid-beta as a drug target, especially early in AD, or the amyloid hypothesis. One criticism is that the solanezumab dose was too low. There were consistent trends toward the solanezumab group having better outcomes compared to the placebo group, but the effect size was low. Coupled with low adverse events reported with the dose used, higher doses of solanezumab potentially could lead to larger effect size and statistically meaningful outcomes without increasing adverse events. Also, it is possible that the treatment still was initiated too late. In response to these criticisms, current trials using solanezumab in cognitively normal subjects with biomarker evidence of AD (A4 trial) have increased the dosage and length of treatment with solanezumab. The A4 trial and the DIAN-TU trial, investigating solanezumab on subjects with familial AD mutations, will be critical in determining whether solanezumab becomes a viable therapy.

Despite the negative results, there are important lessons learned from EXPEDITION 3. It has paved the way for better trial design, including the use of amyloid-beta and tau biomarkers as both study inclusion criteria and outcome measures. Additionally, failure of one anti-amyloid therapy does not mean that all anti-amyloid therapies are destined to fail, such as the ongoing aducanumab trial, as they target different forms of amyloid-beta and hence different aspects of amyloid pathology. Therefore, the journey continues to find the first new AD drug since 2003. ■

ABSTRACT & COMMENTARY

Parsonage-Turner Syndrome: Where's the Lesion?

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: This careful analysis of MRI imaging of the brachial plexus in patients with well-defined Parsonage-Turner Syndrome showed that the lesions are in peripheral branches of the brachial plexus and not in the roots or cords.

SOURCE: Sneag DB, Schneider KR, Wolfe SW, et al. Brachial plexitis or neuritis? MRI features of lesion distribution in Parsonage-Turner syndrome. *Muscle Nerve* 2018 Feb. 20; doi: 10.1002/mus.26108. [Epub ahead of print].

Considered an inflammatory disorder of the brachial plexus affecting children and adults, Parsonage-Turner syndrome (PTS) also is referred to as neuralgic amyotrophy, brachial neuritis, idiopathic brachial plexopathy, brachial plexus neuropathy, and acute brachial radiculitis. As biopsy or autopsy in these cases is rare, pathology and etiology remain speculative, although an immune-mediated process is hypothesized, with up to 50% of patients reporting an antecedent event including strenuous exercise, infection, pregnancy, vaccination, or surgery. Although some patients may have involvement of single or multiple nerves in the limb, resembling mononeuritis or mononeuritis multiplex, the distribution sometimes suggests focal involvement of a part, or parts, of the brachial plexus. Is this anatomically accurate?

To address this question, Sneag et al conducted a retrospective search of the imaging database at the Hospital for Special Surgery in New York, for MRI scans of the brachial plexus in patients with suspected PTS. Only those performed with a 3.0 T magnet and those with fat-suppressed, T2-weighted sequences orthogonal to the longitudinal course of the nerve were collected. All patients who met imaging criteria were reviewed to confirm the diagnosis of PTS based on clinical history, physical examination, and electrodiagnostic findings, the latter encompassing a complete or near complete pattern of denervation, with absent or reduced interference pattern on needle electromyography, and nerve conduction studies showing no evidence of multifocal motor neuropathy or other generalized neuropathy that might mimic PTS. Patients were excluded if comorbidities or alternative diagnoses could not be excluded. Investigators reviewed brachial plexus MRI scans were reviewed at every level of the plexus for fascicular morphology, signal intensity, and size, as well as for edema or fatty infiltration of regional muscles. Side and terminal branches of the plexus and more peripheral nerves also were evaluated for the presence of hourglass constrictions, defined as a short segment of decreased nerve caliber.

Among 87 MRI studies, 35 met MRI inclusion criteria, of which eight were excluded because of alternative diagnoses, including cervical radiculopathy (n = 4), diabetic neuropathy (n = 1), hereditary neuropathy with liability to pressure palsies (n = 1), or insufficient electromyography (EMG) data (n = 2). Of the 27 subjects who met all inclusion criteria, 19 were men and eight were women,

with a mean age of 42 years. EMG revealed abnormalities in 37 nerves, half of which comprised an isolated mononeuropathy, usually the suprascapular nerve, and no abnormality localized to the brachial plexus proper, roots or cords, on electrodiagnostic studies. MRI of the brachial plexus was normal in 24 of 27 patients. Two of the remaining three cases comprised isolated suprascapular nerve involvement clinically, with MRI in one patient demonstrating signal hyperintensity in the suprascapular nerve extending proximally to the extra-foraminal C5 nerve root, 3.5 cm lateral to the neural foramen, and, in the other, signal hyperintensity of the nerve extending into the superior trunk, proximal to the suprascapular nerve take-off. In the third patient, signal hyperintensity was seen in the axillary nerve extending proximally into the posterior cord. Intrinsic constrictions were seen in 32 of 38 nerves, with hyperintensity and enlargement of imaged nerves and muscle denervation edema present in all patients. PTS appears to affect either branches of the brachial plexus or more peripheral nerves rather than the brachial plexus proper.

■ COMMENTARY

No specific treatment exists for PTS. Physical therapy can maintain range of motion but does not hasten recovery. Often, analgesics are required to control pain, but steroids are of no demonstrable benefit. Approximately 60% of patients are left with residual pain or fatigue, even three years post-PTS, and recurrence may be seen in 25%, occurring in a median of just over two years following the initial event. ■

ABSTRACT & COMMENTARY

A Possible New Treatment for HTLV-1-associated Myelopathy

By Joseph E. Safdieh, MD

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

SYNOPSIS: Mogamulizumab reduces central nervous system inflammation and improves spasticity in patients with HTLV-1-associated myelopathy.

SOURCE: Sato T, Coler-Reilly ALG, Yagishita N, et al. Mogamulizumab (anti-CCR4) in HTLV-1-associated myelopathy. *N Engl J Med* 2018;378:529-538.

Human T-lymphotropic virus type 1 (HTLV-1) is a retrovirus that causes a disabling myelopathy. It is also causes adult T-cell leukemia-lymphoma (ATLL). HTLV-1 affects millions worldwide, and is quite prevalent in Caribbean countries. Hence, the associated myelopathy also is known as HTLV-1-associated myelopathy-tropical spastic paraparesis (HAM-TSP). HAM-TSP manifests as a subacute progressive myelopathy with the development of spastic weakness, urinary urgency, and sensory ataxia. Less than 2% of patients with HTLV-1 infection develop HAM-TSP. Currently, there are no established effective therapies for HAM-TSP, and patients eventually become severely disabled.

HTLV-1 is believed to cause myelopathy by producing spinal cord inflammation. HTLV-1 infects CCR4+ T-lymphocytes, converting them into abnormal cells that drive inflammation in the spinal cord. In Japan, the anti-CCR-4-binding monoclonal antibody mogamulizumab is approved for the treatment of ATLL. In this study, Sato et al hypothesized that lower doses of mogamulizumab administered on a regular basis to patients with HAM-TSP could help reduce spinal cord inflammation and improve neurologic symptoms.

Sato et al performed a Phase I and IIa study. Initially, they recruited 21 patients who received a single dose of mogamulizumab and were observed for 85 days. Of those 21 patients, 19 were advanced into the Phase IIa trial, where they were treated with repeat doses every eight weeks for 24 weeks. The primary endpoints were safety and pharmacokinetics. The secondary endpoint was measurement of proviral load in peripheral blood mononuclear cells. Other measures investigated included markers of cerebrospinal fluid (CSF) inflammation (CXCL10 and neopterin) as well as clinical measurements of activities of daily living, spasticity, dysuria, sensory dysfunction, and mobility.

The results of the study demonstrated that the drug did not cause side effects that limited treatment dose. Most common side effects were rash and leukopenia. There were no deaths during the study. Proviral load in peripheral blood mononuclear cells was reduced by 65%. Levels of the two studied inflammatory CSF markers both were reduced significantly with treatment. Very notably, spasticity, as measured by the Ashworth Scale Score, was reduced by almost 80% and motor disability improved by 32%.

■ COMMENTARY

Clearly, this is an important study. There is a serious need for a therapy that can treat patients with HAM-TSP, as current agents are off-label and do not provide significant relief or sustained improvement. Further studies are needed, including a randomized trial of mogamulizumab in patients with HAM-TSP. Suppression of CCR-4 T-cells may lead to serious infections, which is why the study authors used a lower dose of mogamulizumab than used to treat ATLL, a very aggressive form of cancer. However, even at lower doses, longer-term follow-up will be needed to assess safety. It is unclear how long patients would need to be treated and it is possible that treatment would need to be indefinite, further supporting the need for follow-up studies.

Monoclonal antibodies have revolutionized the treatment of many medical disorders, including common and disabling neurologic disorders. We already have seen the approval of monoclonal antibodies for multiple sclerosis (natalizumab, ocrelizumab, alemtuzumab), myasthenia gravis (eculizumab), and giant cell arteritis (tocilizumab). There is also a great deal of anticipation for the calcitonin gene-related peptide monoclonal antibodies in the treatment of migraine. There have been failed trials of monoclonal antibodies, most notably bapineuzumab and solenezumab (see this ALERT, page 61) for Alzheimer's disease. If mogamulizumab succeeds in larger and longer studies, the treatment for yet another previously devastating neurologic disorder will be possible. ■

CME QUESTIONS

1. **Which of the following is *not* true regarding the epidemiology of autoimmune encephalitis and infectious encephalitis?**
   a. Prevalence of autoimmune encephalitis was almost three times higher in African-Americans than Caucasians.
   b. Autoimmune encephalitis has a greater tendency to relapse compared to infectious encephalitis.
   c. Over the span of two decades, 1995-2005 and 2006-2015, the incidence of autoimmune and infectious encephalitis increased three-fold.
   d. There were no differences in ethnic proportionality pertaining to prevalence or incidence of infectious encephalitis.
2. **A 28-year-old woman with occasional migraines without aura and chronic depression maintained on a selective serotonin reuptake inhibitor (SSRI) comes for a second opinion regarding migraine management. Her primary care physician told her she could not take triptan medications for headaches because she is taking an SSRI. What do you advise?**
   a. Agree with the primary care physician and decline to prescribe a triptan.
   b. Discontinue her SSRI and prescribe a triptan as needed.
   c. Reassure her that the medical literature has shown serotonin syndrome to be rare and then prescribe a triptan.
   d. Prescribe a prophylactic medication so she will not need a triptan.
3. **An acute headache in a woman that occurs days after delivery without migraine-like features is most likely caused by which of the following?**
   a. Postdural puncture headache
   b. Migraine without aura
   c. Internal carotid artery dissection
   d. Pre-eclampsia
4. **Which of the following statements is *false* about the EXPEDITION 3 trial investigating solanezumab in Alzheimer's disease?**
   a. Solanezumab is a human monoclonal antibody against soluble amyloid-beta.
   b. Compared to placebo, solanezumab treatment had no significant difference on the decline of cognitive function as measured by ADAS-Cog14.
   c. Compared to placebo, solanezumab treatment had no significant difference on the MRI measures of whole brain or ventricular size.
   d. Compared to placebo, solanezumab treatment had significantly higher number of subjects dropping out of the trial because of adverse events.
5. **Based on recent MRI evidence, Parsonage-Turner syndrome seems to predominantly affect which of the following?**
   a. Trunks of the brachial plexus
   b. Divisions of the brachial plexus
   c. Cords of the brachial plexus
   d. Branches of the brachial plexus

[IN FUTURE ISSUES]

Update on Epilepsy