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Neurology [ALERT®]

Evidence-based summaries of the latest clinical neurology research

ABSTRACT & COMMENTARY

Is it Guillain-Barré or Acute-onset CIDP?

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: Acute inflammatory demyelinating polyneuropathy and acute-onset chronic inflammatory demyelinating polyneuropathy (CIDP) may present with identical clinical pictures and can be differentiated only with the passage of time. CIDP will have a slower course of progression and may involve relapses.

SOURCE: Alessandro L, Rueda JMP, Wilken M, et al. Differences between acute-onset chronic inflammatory demyelinating polyneuropathy and acute inflammatory demyelinating polyneuropathy in adult patients. *J Peripher Nerv Syst* 2018;23:154-158.

Weakness in acute inflammatory demyelinating polyneuropathy (AIDP) develops over several days, reaching maximal deficit within four weeks. However, neurological deficits in chronic inflammatory demyelinating polyneuropathy (CIDP) evolve at a slower pace, progressing over at least a two-month period. Although this temporal demarcation appears straightforward, in clinical practice, differentiating the two disorders early may be difficult, as some CIDP patients, usually children or young adults, present with an acute- or subacute-onset CIDP (A-CIDP) that resembles AIDP and will be recognized only with the passage of time. Might it be possible clinically to differentiate AIDP from A-CIDP earlier?

Alessandro et al conducted a retrospective review of the records of 119 patients, 18 years of age or older, diagnosed with AIDP between January 2006 and July 2017 at the Center for Research on Neuroimmunological Diseases at Raúl Carrea Institute for Neurological Research in Buenos Aires, Argentina. Data collected included medical history; vaccinations within a month prior to disease onset; HIV status; motor, sensory, and autonomic dysfunction; cerebrospinal fluid (CSF) analysis; and electrodiagnostic testing. Patients were classified as AIDP or A-CIDP based on published[1] and electrophysiologic criteria. All patients were followed for at least one year. A statistical analysis comprised Student's *t* test, Fisher's test, and Pearson's $\chi 2$ test.

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Of the 119 patients' records reviewed, 91 satisfied criteria for inclusion in the study, 77 with AIDP and 14 with A-CIDP, of which 69% were male. Mean age (43 years and 55.5 years, respectively) was not significantly different between the two groups. In addition, no difference was found for median Medical Research Council sum score, sensory disturbances, autonomic dysfunction, cranial nerve involvement, CSF cytoalbuminogenic dissociation, HIV status, neoplastic or autoimmune disease, preceding infectious disease or vaccination, rate of respiratory dysfunction, need for mechanical ventilation, hemodynamic instability, intensive care monitoring, or death. However, diabetes mellitus was seen more often in A-CIDP (29% vs. 8%; $P = 0.4$), as were proprioceptive abnormalities (83% vs. 28%; $P < 0.001$) and sensory ataxia (46% vs. 16%; $P = 0.01$). First relapse in A-CIDP patients occurred eight weeks after initial acute presentation, with most (11/14) evolving into CIDP, and few into single (n = 2) or relapsing-remitting (n = 1) disease. Based on this retrospective analysis, AIDP and A-CIDP essentially are indistinguishable.

■ COMMENTARY

First described in 1958 by Austin as a fluctuating, motor-predominant polyneuropathy responsive to corticosteroid treatment, the term chronic inflammatory polyneuropathy (demyelinating was added later) was introduced by Dyck in 1975 in a landmark paper describing 53 personally examined patients. Segmental demyelination, typically paranodal, and remyelination, the pathologic hallmarks, are best seen on teased nerve fiber preparations, with inflammatory, frequently perivascular, infiltrates. Chronic demyelination and remyelination result in onion bulb formation. Although some have suggested that diabetes is a risk factor for developing CIDP, at least two epidemiologic studies have shown this is not the case. In addition to the classic presentation of symmetrical polyneuropathy, subtypes include multifocal CIDP, an upper-limb-predominant asymmetric neuropathy, also known as Lewis-Sumner syndrome or MADSAM (multifocal acquired demyelinating sensory and motor neuropathy), with focal motor and sensory conduction blocks, mildly elevated protein (not as high as classic CIDP), and responsive to corticosteroids (unlike multifocal motor neuropathy with conduction block, which does not) and intravenous immunoglobulin. CIDP may affect only sensory nerve roots, chronic inflammatory sensory polyneuropathy, resulting in sensory ataxia and numbness with mild pain and without weakness.[2] ■

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ABSTRACT & COMMENTARY

Effect of Diet on Hippocampal Volume in a Population at Risk for Alzheimer's Disease

By Lisa Mosconi, PhD

Associate Director, Alzheimer's Prevention Clinic/Department of Neurology, Weill Cornell Medical College

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

SYNOPSIS: Magnetic resonance imaging of the brain in community-dwelling people (average age of 60 years) found that a long-term, high-quality diet was associated with larger hippocampal volumes after an average interval of 11 years.

SOURCE: Akbaraly T, Sexton C, Zsoldos E, et al. Association of long-term diet quality with hippocampal volume: Longitudinal cohort study. *Am J Med* 2018; Jul 26. doi: 10.1016/j.amjmed.2018.07.001. [Epub ahead of print].

Results from many recent studies have supported the beneficial effect of diet and nutrition on the development of cognitive decline and Alzheimer's disease. Researchers have found that diet not only has a therapeutic effect on cognitive function, but also improves mood, cardiovascular risk, weight loss, and insulin resistance. Although researchers have examined how diet affects a variety of cognitive outcomes, such as memory scores and progression to a diagnosis of mild cognitive impairment or Alzheimer's disease, few have examined how diet affects brain biomarkers of Alzheimer's disease, especially among middle-aged, cognitively intact individuals. This information is critical when evaluating diet to prevent brain aging and dementia.

Akbaraly et al examined nutritional quality as a predictor of hippocampal volume, a well-established marker of Alzheimer's disease risk, in a prospective cohort of community-dwelling participants from the Whitehall II study, which was designed to investigate long-term health outcomes, particularly cardiovascular disease prevalence and mortality rates, among 10,308 British civil servants recruited from 1985 to 1988.[1] Participants were 35 to 55 years of age at the beginning of the study. Two-thirds were men and one-third women.

Akbaraly et al focused on a subset of 459 participants who received serial dietary exams and a magnetic resonance imaging (MRI) scan of the brain an average of 11 years after the study began. Investigators asked participants to use food frequency questionnaires to track their food patterns over the previous 11 years, and conducted examinations approximately every five years. MRI scans were performed once, in 2015-2016. At the time, participants were an average of 60 years of age and 19% were female.

The food frequency questionnaires measured intake of 11 components (foods and nutrients), including six components for which high intakes are considered ideal (e.g., vegetables, fruit, whole grains, nuts and legumes, long-chain omega-3 fats, and total polyunsaturated fatty acids) and five components for which avoidance or low intake is considered ideal (e.g., sugar, sweetened drinks and fruit juice, red and processed meat, trans-fat, and sodium). Based on the intake of these foods and nutrients, the researchers calculated Alternative Healthy Eating Index 2010 (AHEI) scores for each participant at each visit.[2] A higher score was associated with a higher-quality nutritional diet. Based on AHEI scores, participants were divided into those who maintained a healthy diet, those who maintained a poor-quality diet, those who improved the quality of their diets, and those whose diets got worse over time.

After adjusting for age, sex, and total calorie intake, higher AHEI scores were significantly associated with larger hippocampal volumes. Each one-point increment in AHEI scores was associated with an increase in hippocampal volume by up to 92.5 cc. This effect was independent of a variety of possible confounding factors, such as occupational grade, physical activity, smoking habits, presence of cardiometabolic disorders, cognitive impairment, and depressive symptoms. Additionally, participants who maintained a healthy diet or improved their diet throughout the course of the study had larger hippocampal volumes compared to those who ate a poor-quality diet.

[Participants who maintained a healthy diet or improved their diet throughout the course of the study had larger hippocampal volumes compared to those who ate a poor-quality diet.]

■ COMMENTARY

These findings are consistent with previous work showing that short-term diet quality is associated with preserved brain biomarkers of Alzheimer's disease in middle-aged and older adults.[3,4] To further support these associations, the authors of two randomized, controlled trials found additional data to support the importance of nutrition for preventing Alzheimer's disease. In the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability study, researchers found that a lifestyle intervention including nutrition, exercise, and cognitive training reduced the risk of cognitive decline.[5] In the second trial, researchers found that following a Mediterranean-style diet enriched with extra virgin olive oil or a handful of nuts each day improved memory, attention, and executive function compared to a low-fat diet.[6] Although additional randomized, controlled trials are needed, recommending targeted dietary interventions in midlife is evidence-based and safe for reducing the risk of cognitive decline and Alzheimer's dementia. ■

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ABSTRACT & COMMENTARY

Quality of Life After Focused Ultrasound Thalamotomy in Parkinson's Disease

By Harini Sarva, MD

Assistant Professor of Clinical Neurology, Weill Cornell Medical College

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

SYNOPSIS: Mood, cognitive, and behavioral changes in tremor-predominant Parkinson's disease patients, three and 12 months after receiving MRI-guided focused ultrasound thalamotomy, were correlated with quality of life more than the severity of tremor reduction.

SOURCE: Sperling SA, Shah BB, Barrett MJ, et al. Focused ultrasound thalamotomy in Parkinson's disease: Nonmotor outcomes and quality of life. *Neurology* 2018;91:e1275-e1284.

Magnetic resonance imaging-guided focused ultrasound (MRIgFUS) lesioning of the VIM thalamus is effective in treating appendicular essential tremor and now is being investigated to assess its efficacy in Parkinson's disease (PD) tremor. Although initial studies of PD tremor have been encouraging, the long-term cognitive, behavioral, and quality-of-life effects of the thalamotomy are unknown. In this study, cognition, behavioral changes, and mood were assessed three months after MRIgFUS thalamotomy for tremor-predominant PD. Secondary outcomes included changes in these domains after three and 12 months. Postoperative quality-of-life assessments were performed to understand the effects of non-motor symptoms and tremor reduction on patient well-being. The sample group of subjects (n = 27) were derived from the investigators' pilot randomized, sham-controlled MRIgFUS thalamotomy study for PD tremor, which was published in 2017. Twenty subjects were assigned to active treatment and seven to sham. After the three-month crossover period, six from the sham arm crossed over to the active group. In addition to PD and tremor rating scales, the patients underwent a comprehensive neuropsychological battery, which included tests for verbal fluency, frontal dysfunction, and quality of life.

[Although MRI-guided focused ultrasound thalamotomy has been shown to be safe in essential tremor, its overall effects on cognition in Parkinson's disease are unknown, despite preliminary positive results.]

Baseline demographic, motor, and non-motor characteristics were not statistically significant between the active and sham groups. There were no differences in overall cognitive performance or assessments of mood from baseline at three months and at 12 months. There were no statistically significant differences in cognitive or psychiatric assessments between those who received the treatment initially compared to the six who crossed over after receiving sham, but verbal fluency declined. Quality of life improved postoperatively at three months and at 12 months. However, quality-of-life changes did not correlate to tremor severity but with mood disorders, level of functionality, and Unified Parkinson's Disease Rating Scale motor subscale scores, which accounts for all motor features of PD.

■ COMMENTARY

Prior literature describing neuropsychiatric effects following lesioning procedures has been mixed, with

some showing decline and others no decline. This study demonstrates cognitive and psychiatric stability in patients receiving MRIgFUS thalamotomy for PD tremor both at three and 12 months post-procedure. Although this is encouraging, there are several important considerations. The sample size was small. Tremor-predominant PD patients who were not afflicted with a fast cognitive decline, in comparison to the postural instability gait disorder subtypes, were studied. Thus, it would be important to study this latter subtype, which more commonly is associated with cognitive decline, to allow for generalizability of these data. A number of patients were lost to follow-up at 12 months, further reducing predictability in cognition and mood at longer time points. With the use of more advanced MRI technology, such as tractography and other functional imaging, as well as the detailed neuropsychological battery and longer follow-up, subsequent studies may provide a better assessment of the non-motor effects of this lesioning procedure. The lesion target (thalamus vs. pallidum) also may play a role in determining neuropsychiatric stability long term, but further data are required.

Although MRIgFUS thalamotomy has been shown to be safe in essential tremor, its overall effects on cognition in PD are unknown, despite the preliminary positive results. Thus, larger studies involving complete neuropsychological batteries are necessary to determine the long-term sequelae of noninvasive lesioning procedures in PD. ■

ABSTRACT & COMMENTARY

Costs and Consequences of Chronic Pain Among U.S. Adults

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: Chronic and disabling pain is a common and serious cause of morbidity among U.S. adults.

SOURCE: Dahlhamer J, Lucas J, Zelaya C, et al. Prevalence of chronic pain and high-impact pain among adults – United States, 2016. *Morbid Mortal Weekly Rep* 2018;67:1001-1006.

Chronic pain is one of the most common reasons adults seek medical care. Chronic pain is associated with multiple physical and psychological conditions that contribute to restricted mobility and daily activities, dependence on opioids, anxiety and depression, and poor perceived health or reduced quality of life. In turn, this leads to high healthcare costs and lost productivity. One of the nation's science-based health objectives is to decrease the prevalence of adults experiencing high-impact chronic pain.

To estimate the prevalence of chronic pain in the United States, the Centers for Disease Control and Prevention (CDC) analyzed data from the 2016 National Health Interview Survey. Chronic pain was defined as pain on most days or every day in the past six months. High-impact chronic pain was defined as chronic pain that limited life or work activities on most days or every day during the last six months. Based on this survey, about 50 million (20.4%) U.S. adults had chronic pain, with 19.6 million (8.0%) having high-impact chronic pain. Higher prevalence of chronic pain and chronic high-impact pain was seen in women, older adults, adults who previously but not currently were employed, adults living in poverty, those with public health insurance, and those in rural regions. The age-adjusted prevalence of chronic pain was significantly lower among adults with a college degree. There were no significant racial or ethnic differences in those with chronic high-impact pain, although non-Hispanic white adults reported more chronic pain than other ethnic/racial subgroups.

Annually, chronic pain contributes to an estimated $560 billion in direct medical costs, lost productivity, and disability programs. Identifying populations at risk is the first step for developing targeted interventions for pain management.

■ COMMENTARY

Chronic pain is a common, multidimensional medical condition that contributes to high healthcare costs, lost productivity, and poor quality of life, and fuels the current opioid epidemic. High-impact chronic pain refers to pain that is frequent and disabling. The results of this study help quantify the prevalence of high-impact chronic pain and, by identifying specific patient populations at risk, will help inform targeted interventions. ■

Stroke Alert

By Matthew E. Fink, MD

Thrombolysis for 'Wake-up' Stroke

SOURCE: Thomalla G, Simonsen CZ, Boutitie F, et al; for the WAKE-UP Investigators. MRI-guided thrombolysis for stroke with unknown time of onset. *N Engl J Med* 2018;379:611-622.

Current guidelines for the use of intravenous thrombolysis state that this treatment should be given only if the onset of stroke symptoms clearly can be determined as occurring less than 4.5 hours before the time of administration. Currently, if the last known normal time cannot be ascertained, then intravenous thrombolysis is not recommended. In this multicenter randomized trial, patients who had an unknown time of onset for ischemic stroke were treated with either intravenous alteplase or placebo. All of the patients had an acute ischemic lesion that was visible on MRI diffusion-weighted imaging, but had no hyperintensity on FLAIR images, which indicated that the stroke occurred approximately within the previous 4.5 hours. The primary endpoint was a favorable outcome, defined as a score of 0 or 1 on the modified-Rankin scale at 90 days. The secondary outcome was that alteplase treatment would lead to a lower score on the modified-Rankin scale, indicating a better neurological outcome.

The researchers anticipated that 800 patients would be enrolled, but the trial was stopped after enrollment of 503 patients because of cessation of funding. Eighty-nine percent of all patients were diagnosed with ischemic stroke after they awakened in the morning, and the last known normal was more than seven hours earlier. The researchers randomly assigned 254 patients to alteplase and 249 to placebo. A favorable outcome at 90 days was reported in 53.3% of the alteplase group and in 41.8% in the placebo group (adjusted odds ratio, 1.61; P = 0.02). The median score on the modified Rankin scale at 90 days was 1 in the alteplase group and 2 in the placebo group (P =0.003). There were 10 deaths in the alteplase group and three deaths in the placebo group, which most likely were attributed to symptomatic intracranial hemorrhage, which occurred in 2% of the alteplase group and 0.4% in the placebo group. In conclusion, in patients with acute ischemic stroke of unknown time of onset, a mismatch between diffusion-weighted imaging and FLAIR imaging in the region of ischemia resulted in better functional outcome if treated with intravenous alteplase, but with more symptomatic intracranial hemorrhages. ■

Ultraearly Intravenous Thrombolysis for Acute Ischemic Stroke

SOURCE: Tsivgoulis G, Geisler F, Katsanos AH, et al. Ultraearly intravenous thrombolysis for acute ischemic stroke in mobile stroke unit and hospital settings. A comparative analysis. *Stroke* 2018;49:1996-1999.

Time from onset of acute ischemic stroke until treatment with intravenous thrombolysis is the critical factor that determines the likelihood of both successful reperfusion as well as long-term functional outcome. However, only a small fraction of patients with acute ischemic stroke receive intravenous thrombolysis treatment within the first 60 minutes from symptom onset, also known as the "golden" hour when this treatment is presumed to have the greatest benefit. The advancement of mobile stroke treatment units (MSU), first in Europe and then in North America, has resulted in a dramatic increase in the number of patients treated within the first 60 minutes, but whether this results in equivalent outcome compared to hospital care is unknown.

The investigators in Berlin, with a long history of mobile stroke treatment unit experience, identified and compared a cohort of MSU-treated patients with those treated in the hospital. They identified 117 MSU patients treated within the first 60 minutes (38.4% of 305 MSU treated patients) and compared them with 136 hospital-setting patients treated within 60 minutes (0.9% of 15,591 hospital-treated patients). They evaluated outcomes at 90 days. They found no significant differences between the groups, with favorable functional outcome in 51.3% of MSU-treated patients vs. 46.2% of hospital-treated patients, with mortality in 7.7% of MSU patients vs. 9.9% of hospital-treated patients. At three months, there was no difference in the distribution of the modified Rankin scale scores between the two groups.

Tsivgoulis et al concluded that the safety and efficacy of ultraearly intravenous thrombolysis for patients with acute ischemic stroke is the same whether used on an MSU or in the hospital setting. However, it is 40 times more likely that an MSU-treated patient

will be treated within the first 60 minutes compared to a hospital-setting patient. ■

Should Aspirin Be Used for Primary Prevention of Cardiovascular Events?

SOURCES: McNeil JJ, Woods RL, Nelson MR, et al; for the ASPREE Investigator Group. Effect of aspirin on disability-free survival in the healthy elderly. *N Engl J Med* 2018; Sep 16. doi: 10.1056/NEJMoa1800722. [Epub ahead of print].

McNeil JJ, Woods RL, Nelson MR, et al; for the ASPREE Investigator Group. Effect of aspirin on cardiovascular events and bleeding in the healthy elderly. *N Engl J Med* 2018; Sep 16. doi: 10.1056/NEJMoa1805819. [Epub ahead of print].

McNeill JJ, Woods RL, Nelson MR, et al; for the ASPREE Investigator Group. Effect of aspirin on all-cause mortality in the healthy elderly. *N Engl J Med* 2018, Sep 16. doi: 10.1056/NEJMoa1803955. [Epub ahead of print].

In a remarkable series of three articles published in the Oct. 18, 2018, issue of the *New England Journal of Medicine*, McNeil and collaborators reported on the effects of aspirin as primary prevention for cardiovascular disease in a cohort of healthy elderly people. These studies are of particular interest to neurologists, since much of our practice is related to stroke prevention, both primary and secondary, and we often are asked by patients and their families, as well as referring physicians, if patients should take daily aspirin for stroke prevention.

In these three studies, almost 20,000 persons (median age of 74 years) were enrolled and assigned randomly to receive aspirin or placebo daily for primary prevention. Fifty-six percent of the participants were women, 8.7% were non-white, and 11% reported previous regular aspirin use. The trial was terminated at a median of 4.7 years of follow-up when it was determined that daily aspirin use showed no benefit regarding the primary endpoints. Primary and secondary endpoints included the rate of composite death, dementia, physical disability, and cardiovascular events, which included fatal coronary heart disease, nonfatal myocardial infarction, fatal or nonfatal stroke, and hospitalization for heart failure. In addition, the investigators examined the effects of daily aspirin on all-cause mortality in this same group of healthy older adults.

In light of the generally accepted view that daily aspirin has many health benefits, the results of this study revealed that aspirin use in healthy elderly persons did not prolong disability-free survival over a five-year period but resulted in a higher rate of major hemorrhages compared to placebo. In addition, the use of low-dose aspirin as primary prevention in elderly adults to prevent cardiovascular

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events, including stroke, did not result in a significantly lower risk of cardiovascular disease, but did result in an increased rate of major hemorrhages.

When evaluating all-cause mortality, healthy older adults who received daily aspirin had a higher all-cause mortality that was attributed primarily to cancer-related deaths. The conclusion from this series of groundbreaking studies is that primary prevention of cardiovascular disease and death by using daily low-dose aspirin is not recommended and should be reserved for those instances in which secondary prevention has been demonstrated to be effective in randomized clinical trials. All neurologists should take note of these studies, which significantly affect our practice and our patients. ■

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3. Pass the online test with a score of 100%; you will be allowed to answer the questions as many times as needed to achieve a score of 100%.

4. After completing the test, a credit letter will be emailed to you instantly.

5. Twice yearly after the test, your browser will be directed to an activity evaluation form, which must be completed to receive your credit letter.

CME QUESTIONS

1. **Acute inflammatory demyelinating polyneuropathy (AIDP) may be differentiated from acute-onset chronic inflammatory demyelinating polyneuropathy (A-CIDP) by which of the following?**
   a. The presence of diabetes in AIDP
   b. Sensory ataxia is more profound and frequent in AIDP
   c. Proprioceptive abnormalities are more profound and frequent in AIDP
   d. None of the above

2. **Which of the following food categories is *not* part of a high-quality diet?**
   a. Fresh fruits and vegetables
   b. Nuts and legumes
   c. Sweet fruit juices
   d. Whole grains

3. **Which of the following is *false* regarding MRIgFUS thalamotomy for Parkinson's disease?**
   a. MRIgFUS is effective in treating essential tremor.
   b. Verbal fluency declined in this study.
   c. Tremor was the most important quality of life indicator.
   d. Quality of life correlated with mood and functionality measures.

4. **Which of the following is a characteristic of patients with chronic high-impact pain?**
   a. Female
   b. Older
   c. Higher educational level
   d. Not currently employed

5. **Acute ischemic stroke of undetermined time of onset must not be treated with intravenous thrombolysis**
   a. True
   b. False

6. **Mobile stroke units are treating a higher proportion of patients within the first golden hour compared to hospital-based treatment.**
   a. True
   b. False

7. **Aspirin has been demonstrated to be effective in reducing the rate of recurrent stroke in patients who have suffered a transient ischemic attack or ischemic stroke.**
   a. True
   b. False

[IN FUTURE ISSUES]

Update on Movement Disorders