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Neurology [ALERT®]

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ABSTRACT & COMMENTARY

Anticonvulsant Prescribing Habits and Declining Teratogenesis: The Changing Landscape of Pregnancy and Epilepsy

By Padmaja Kandula, MD

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

SYNOPSIS: These authors analyzed data from a long-standing prospective cohort to study changes in prescribing habits and pregnancy outcomes following restriction on the use of valproic acid in women of child-bearing potential. Declining use of valproate and carbamazepine was associated with a decline in teratogenesis.

SOURCE: Tomson T, Battino D, Bonizzoni E, et al; EURAP Study Group. Declining malformation rates with changed antiepileptic drug prescribing: An observational study. *Neurology* 2019;93:e831-e840.

Since the initial publication of the 2009 American Academy of Neurology practice parameters[1] and NEAD study[2] (fetal antiepileptic drug exposure and cognitive outcomes), there has been increasing interest in both structural and cognitive teratogenesis with regard to anticonvulsant use. The global impact of both the U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA) efforts to tighten the restrictions on the use of valproic acid has changed clinician prescription patterns with a gradual decline of valproic acid use during pregnancy. This decline has been mirrored across several large-scale pregnancy registries. In this article, the authors focused on analyzing pregnancy outcomes from EURAP (European anti-epileptic pregnancy registry) during the 14-year period (2000-2013) preceding the EMA's introduction of further restrictions on valproic acid use.

The EURAP registry was established in 1999 and has involved 42 countries. Previously registered patients included pregnancies exposed to anticonvulsants at conception and enrolled within 16 weeks of gestation. Information on demographics, type of epilepsy, seizure frequency, comorbidities, family history of

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major congenital malformations, and drug treatment previously were obtained in early pregnancy per registry protocol. Follow-up data after each trimester, at birth, and one year after birth were collected by the treating physician and transferred online to a national coordinator in Italy. The authors' analysis tracks the changes in anticonvulsant use and corresponding teratogenic outcomes for conception between the years 2000 and 2013. Those patients with incomplete medical reports or lost to follow-up were excluded. Intrauterine deaths, abortions, and pregnancies complicated by chromosomal and genetic abnormalities were excluded.

Data regarding seizure classification, family history of major congenital malformation, and folate use (initiated at a minimum dosage of 0.4 mg/d consistently at least three months before conception) were extrapolated and analyzed. Information on obstetrical outcomes and occurrence of convulsions during pregnancy were obtained from reporting physicians. To calculate frequencies of major congenital malformations (MCMs), the numerator was the sum of all live births plus pregnancy losses with confirmed MCMs, while the denominator included live births, pregnancies terminated electively for MCMs, and perinatal deaths.

Pregnancies then were divided into three groups based on the year of conception (2000-2005, 2006-2009, and 2010-2013) to analyze time trends. The first epoch, 2000 through 2005, was selected as the reference prior to the first set of important studies demonstrating increased risks with valproic acid published in 2004 and 2005. A second wave of influential studies providing comparative data on teratogenic effects of valproic acid were subsequently published between 2009 and 2011, hence supporting the split of time periods of 2006-2009 (pre-second-wave publications) and 2010-2013 (post-second-wave publications).

In total, 10,291 pregnancies met the criteria for inclusion in the analysis of treatment changes and seizure control, whereas 9,023 pregnancies met criteria for analysis of teratogenic outcomes.

Overall, the proportion of pregnancies with appropriate folic acid supplementation increased over time, but still remained below 50% throughout the 14-year period. The proportion of pregnancies exposed to anticonvulsant monotherapy was similar across all three periods (80.4-81.6%). However, a notable decline in the use of specific anticonvulsants, such as valproic acid (26% to 6%) and carbamazepine (41% to 13.5%), and an increase in the use of lamotrigine and levetiracetam were noted. The use of valproic acid in combination therapy also decreased markedly from the first to the second and third time periods.

The prevalence of MCMs with any monotherapy exposure decreased from 6.0% during 2000-2005 to 4.4% during 2010-2013. With regard to polytherapy, there was also a comparable reduction of 8.3% to 6.1% during 2000-2005 and 2010-2013, respectively. With regard to specific MCMs, an overall reduction for all subtypes was noted, with the exception of those with renal malformations and for multiple MCMs. There were no clinically significant changes in convulsion rate between the three time periods.

■ COMMENTARY

Overall, the study demonstrates a declining trend for the prevalence of MCMs over the 14-year time period. Adjustment for changes in anticonvulsant treatment resulted in elimination of the overall trend, suggesting that improved malformation outcomes were directly related to changes in anticonvulsant use and exposure, namely decreased use of both valproic acid and carbamazepine. Other smaller registries, including the Australian registry and United Kingdom and Ireland registry, found an overall reduction in prescribing of both valproic acid and carbamazepine, but no associated clinically significant improvement in teratogenic outcomes. Despite declining use of first-generation anticonvulsants, seizure control remained unchanged, suggesting equivalent efficacy of second-generation anticonvulsants with a better side effect and teratogenic profile. Further large-scale registries with prospective pregnancies are needed to verify the initial promising results of this analysis. In addition, data regarding long-term cognitive teratogenesis also are critical with regard to counseling women of child-bearing age optimally. ■

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prospective observational study. *Lancet Neurol* 2013;12:244-252.
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ABSTRACT & COMMENTARY

Effects of Probiotics on Cognition and Fall Risk in Patients With Cirrhosis

By Neal S. Parikh, MD, MS

Assistant Professor of Neurology, Weill Cornell Medical College

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

SYNOPSIS: Patients with cirrhosis and mild cognitive impairment and falls were randomized to a probiotic formulation vs. placebo. Probiotic treatment improved cognitive outcomes and reduced the risk of falls.

SOURCE: Román, E, Nieto JC, Gely C, et al. Effect of a multistrain probiotic on cognitive function and risk of falls in patients with cirrhosis: A randomized trial. *Hepatol Commun* 2019;3:632-645.

Hepatic encephalopathy is a hallmark feature of decompensated liver cirrhosis. Cognitive impairment in the form of minimal or covert hepatic encephalopathy also is common in cirrhosis without decompensation. Individuals with cirrhosis and cognitive impairment have poor outcomes, including traffic accidents and falls.

Cognitive impairment in cirrhosis is thought to be caused by hyperammonemia and neuroinflammation. Gut dysbiosis, or the disruption of a healthy gut microbiome, is an area of increasing research interest as it pertains to vascular and cognitive disorders. In cirrhosis, dysbiosis may contribute to systemic inflammation when there is a high burden of pathological bacterial translocation through a disrupted intestinal barrier. For these reasons, Román and colleagues and other research groups have identified the gut microbiome as a potential target for the treatment of cognitive impairment in patients with cirrhosis. Several prior studies demonstrated a favorable effect of probiotics on cognitive measures in this population.

Prior studies focused on the prevention and amelioration of hepatic encephalopathy, whereas Román and colleagues shifted their focus to include fall prevention. They hypothesized that multistrain probiotic supplementation would decrease fall risk in part through improved cognition. Secondarily, they hypothesized that probiotic supplementation would decrease systemic inflammation and intestinal barrier disruption. They did not perform explicit tests of mediation to evaluate these hypotheses.

The authors included consecutive patients with cirrhosis and mild cognitive dysfunction and/or prior falls from a single center. Cognitive dysfunction was defined using the Psychometric Hepatic Encephalopathy Score (PHES), which is a gold standard, comprehensive, validated battery for the assessment of hepatic encephalopathy. Importantly, they excluded patients with overt hepatic encephalopathy, active alcohol users, and those on treatment for hepatic encephalopathy.

Patients were randomized to a probiotic or placebo for 12 weeks. They were evaluated at baseline, after 12 weeks of treatment, and eight weeks after the end of treatment. Key clinical outcomes were cognitive function using the PHES, risk of falls using validated gait metrics, and incidence of falls. Additionally, they measured C-reactive protein (CRP), tumor necrosis factor-alpha (TNF-α), interleukins 6 and 10, neutrophil oxidative reserve, and markers of intestinal barrier integrity.

They screened 279 patients to randomize 36. The two groups were well-balanced. Overall, two patients (6%) died during the short study period. Cognitive function improved over 12 weeks with probiotic treatment ($P = 0.006$) but not with placebo. Similarly, patients randomized to probiotic treatment had significantly improved gait by two parameters, without changes in the placebo-treated patients. While the study lacked the power to detect statistically significant differences in incident falls, probiotic treatment resulted in nominally fewer falls (0 vs. 4; $P = 0.10$). They also lacked power for safety outcomes, but did not detect a difference in serious events.

These findings correlated with reductions in systemic inflammation as measured by CRP and TNF-α, in addition to improved neutrophil oxidative reserve, among only probiotic-treated patients. In parallel, probiotic treatment decreased markers of intestinal barrier disruption. The authors concluded that probiotic treatment may improve cognition and decrease falls in patients with cirrhosis, perhaps through amelioration

of pathological bacterial translocation, intestinal barrier breakdown, and systemic inflammation.

■ COMMENTARY

As the authors acknowledged, the small sample size is a key limitation. However, their study was elegant and rigorous. The found a consistent direction of effect across multiple complementary outcomes, which increases the validity of their results. The authors alleged that their exacting exclusion criteria — excluding those with overt hepatic encephalopathy — was a limitation. While this certainly limits generalizability, their selection criteria had a fortuitous outcome: They demonstrated the effectiveness of probiotic treatment among patients with minimal or covert hepatic encephalopathy. This is important because minimal and covert encephalopathy are far more common and present earlier in cirrhosis. These patients have a longer period during which to derive cognitive and fall-related safety benefits. In this light, the findings of this study may, in fact, have more clinical translational potential. With increasing interest in understanding the role of chronic liver diseases in cognitive impairment, these findings may have therapeutic potential in a larger population than the authors anticipated. Further validation of their findings in patients with milder chronic liver diseases may yield novel opportunities for the treatment of cognitive impairment and the prevention of falls. ■

ABSTRACT & COMMENTARY

Lifestyle and Environmental Risk Factors for Chronic Inflammatory Demyelinating Polyradiculoneuropathy

By Michael Rubin, MD

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Dr. Rubin reports he is a consultant for Merck Sharp & Dohme Corp.

SYNOPSIS: In a large Italian database-derived, case-control study of dietary and environmental factors, antecedent infections and diet appeared to influence the onset and course of chronic inflammatory demyelinating polyradiculoneuropathy. The diagnosis and treatment of this disorder remain a challenge.

SOURCE: Doneddua PE, Bianchib E, Cocito D, et al. Risk factors for chronic inflammatory demyelinating polyradiculoneuropathy (CIDP): Antecedent events, lifestyle and dietary habits. Data from the Italian CIDP Database. *Eur J Neurol* 2019 doi:10.1111/ene.14044. [Epub ahead of print].

Although the pathogenesis of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) remains to be clarified, an autoimmune origin is suspected, with multiple triggers, and with both cellular and humoral components of the immune system contributing. Specific antigens have not been identified, but IgG4 subclass antibodies to neurofascin and contactin, critical structural elements of the paranodal loop attachment to the axolemma, have been reported in small numbers of CIDP patients. They appear to target paranodal proteins, disrupting axon-glial junctions, leading to nerve conduction slowing. Do lifestyle habits, environmental factors, or antecedent infections influence CIDP development, presentation, or clinical course, as they do in other autoimmune diseases?

Doneddua et al used an Italian, CIDP-patient, web-based database to collect information about modifiable environmental factors, antecedent infections, and vaccinations in CIDP patients, with their partners chosen as controls. They performed a gender-matched analysis using randomly selected controls for a 1:1 patient:control ratio. CIDP was diagnosed using European Federation of Neurological Societies/Peripheral Nerve Society (EFNS/PNS) criteria, and at enrollment all eligible patients underwent detailed history. Data on the occurrence of antecedent infection up to 42 days prior to CIDP onset were collected, as was information on diet, smoking habits, alcohol and coffee consumption, toxic exposure, recreational drug use, dietary regimen, and consumption frequency of a variety of foods, including pasta, rice, meat, raw meat, white meat, fish, vegetables, fruit, cheese, eggs, sweets, coffee, tea, milk, and soft drinks. Only those who reported no change in lifestyle habits after CIDP onset were included in the analysis.

Data on 323 patients (109 women and 214 men) and 266 controls (180 women and 86 men) were available, of which 195 cases and 195 sex-matched controls were used for analysis. Eating fish at least once weekly or rice thrice weekly appeared to decrease CIDP risk, whereas antecedent infection or vaccination within 42 days prior to CIDP onset was reported in 12% and 1.5% of patients, respectively. Those with prior infection more often had CIDP with acute onset and cranial nerve involvement. Antecedent events were seen in 15.5%

(n = 63) overall, including a flu-like syndrome (8%), upper respiratory or gastrointestinal infection (2% each), swine-flu vaccination (1.5%), surgery (1%), or trauma (0.5%). Diet and antecedent infection may influence CIDP risk and clinical presentation, but other antecedent events are unlikely to play a role.

■ COMMENTARY

While the etiology remains a mystery in CIDP, making the diagnosis and administering adequate treatment appear to be a challenge as well. Using a self-administered 42-item questionnaire, the investigators performed a quantitative, cross-sectional survey of 100 experienced community neurologists who manage CIDP, representing 31 of the 50 states in the United States, from both university- and non-university affiliated practices. They found that EFNS/PNS guidelines for CIDP diagnosis were used by only 13%, and approximately 50% endorsed electrodiagnostic criteria that did not support a diagnosis of CIDP. Pain or fatigue were identified among 37% and 35% of neurologists, respectively, as indicators of medically significant inflammatory neuropathies requiring treatment, although neither is a reliable prognostic indicator nor generally used to guide dosing decision making. Treatment often was inadequate, with 43% offering less than the recommended loading dose of intravenous immune globulin (IVIG), or excessive, with 24% recommending both steroids and IVIG together as a first-line treatment. Further research is needed to uncover the cause of CIDP, and additional education is needed for its correct diagnosis and treatment.[1] ■

REFERENCE

1. Gelinas D, Katz J, Nisbet P, England JD. Current practice patterns in CIDP: A cross-sectional survey of neurologists in the United States. *J Neuro Sci* 2019;397:84-91.

ABSTRACT & COMMENTARY

Adiposity Is Related to Cerebrovascular and Brain Volumetry Outcomes

By Makoto Ishii, MD, PhD

Assistant Professor of Neuroscience and Neurology, Feil Family Brain and Mind Research Institute, Department of Neurology, Weill Cornell Medical College

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

SYNOPSIS: In this prospective longitudinal study investigating the potential mechanistic link between adiposity and vascular cognitive impairment, anthropometric and metabolic hormone adiposity predictors were differentially associated with cerebrovascular and brain volumetry outcomes by sex in older individuals.

SOURCE: Arnoldussen IAC, Gustafson DR, Leijsen EMC, et al. Adiposity is related to cerebrovascular and brain volumetry outcomes in the RUN DMC study. *Neurology* 2019;93:e864-e878.

With a rapidly aging population and no effective interventions for late-onset dementia, there is a strong interest in identifying modifiable dementia risk factors. Obesity in midlife is associated with an increased risk of cerebrovascular events and late-onset dementia; however, the mechanisms linking obesity to vascular cognitive impairment have not been entirely elucidated. Therefore, the study investigators examined in a prospective longitudinal study (the Radboud University Nijmegen Diffusion Tensor and Magnetic Resonance Imaging Cohort, RUN DMC) whether anthropometric adiposity predictors and metabolic adiposity hormones were associated with cerebral small vessel disease (CSVD) markers and brain volumetry measures.

Adults without dementia were recruited from consecutive patients referred to the Department of Neurology at Radboud University (Netherlands) between October 2002 and November 2006 because of CSVD symptoms, including transient ischemic attack, lacunar syndromes, and subacute manifestations (e.g., cognitive and gait disturbances). Study participants were evaluated at baseline and nine-year follow-up. Anthropometric measures of adiposity including body mass index (BMI) and waist circumference (WC) were obtained at baseline and follow-up visits, while adiposity hormones leptin and adiponectin were measured in the serum only at the baseline visit. The investigators obtained 1.5T MRI scans at both visits and analyzed for CSVD markers and regional brain volumes. Dementia screening using DSM-IV criteria was performed at the follow-up visit. Multivariable regression analyses examined the cross-sectional and longitudinal associations between adiposity and brain MRI measures.

A total of 503 subjects were recruited at baseline (56.5% male; mean age 65.6 ± 8.8 years); 209 subjects were lost to follow-up. At the follow-up visit, 65 subjects were diagnosed with dementia. In cross-sectional analyses, there were significant sex differences in the association

of adiposity measures with CSVD outcome measures. In men, leptin was protective for CSVD outcomes (lower white matter intensities [WMH] and lower odds of lacunes) at baseline, while obese WC decreased the odds of microbleeds and lacunes at the nine-year follow-up. In women, having high BMI or an obese WC was associated with the presence of lacunes at the follow-up visit.

For cross-sectional analyses of brain volumetry outcomes, higher adiposity measures were associated with lower brain volumes when men and women were pooled together for the analyses. However, there were significant sex differences, with men having stronger associations than women. At baseline, in men, higher BMI, WC, and leptin levels were associated with lower grey matter volumes [GMV] and total brain volumes [TBV], and increasing BMI and WC were associated with lower hippocampal volumes [HV]. At the follow-up visit, cross-sectional analyses found higher BMI was associated with lower GMV in men. These associations were not significant for women.

Longitudinal analyses of baseline adiposity predictors found no significant associations with CSVD or brain volumetry outcomes. However, a baseline obese WC was associated over nine years with decreasing HV in men but not women and increasing WMH when men and women were pooled together. Finally, there were no associations between adiposity measures and dementia.

■ COMMENTARY

The RUN DMC study investigators sought to address several important questions regarding the mechanistic link between adiposity and dementia focusing on brain imaging measures of CSVD and regional volumes. Despite conflicting results, there were several notable findings. First, significant sex differences were found, including some findings that were contradictory between men and women. For example, adiposity measures were protective for CSVD outcomes in men but detrimental in women. Furthermore, higher adiposity measures were significantly associated with lower brain volumes in men but not in women. The reasons for the sex differences are not clear and require verification in additional cohorts. Also, in men, adiposity predictors had a detrimental effect on regional brain volumes despite the protective effect on CSVD outcomes. This suggests that there is not a simple direct relationship between CSVD and brain volume. In addition, adiposity may be beneficial in some circumstances but detrimental in others. One intriguing possibility is that the association between adiposity predictors and brain outcomes may be dependent on age, as other studies have found that midlife obesity is associated with reduced GMV and increased dementia risk, whereas later-life overweight and obesity are associated with decreased dementia risk. Unfortunately, the current study does not allow for the evaluation of life-course trajectories necessary to test this hypothesis. Finally, none of the adiposity measures were associated with dementia, but this may be due to the relatively small number of individuals who developed dementia during the follow-up period.

The overall study design is strong with a relatively large number of well-characterized participants and outcome measures at baseline and after nine-year follow-up; however, there are several limitations. First, blood was not collected at follow-up to study the longitudinal effects of leptin or adiponectin. Second, sociodemographic and health status information were not updated at follow-up. Third, the findings from this study may not be generalizable, as all participants were diagnosed with CSVD and from Northern European ancestry. Fourth, no cognitive measures were investigated. Additionally, the investigators found differential loss to follow-up due to death, where those individuals who died during follow-up had at baseline higher adiposity predictors, more cardiovascular risk factors, lower brain volumes, and worse CSVD outcome measures, suggesting survival bias. While the results from the RUN DMC study are conflicting at times and more questions were generated than answered, the authors highlighted the critical need for additional well-designed investigations looking into the relationship between adiposity and dementia, with a particular emphasis on sex differences. ■

ABSTRACT & COMMENTARY

Are Steroids Indicated in the Treatment of Acute Spinal Cord Injury?

By Santosh Murthy, MD

Assistant Professor of Neurology, Weill Cornell Medical College

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

SYNOPSIS: In a comprehensive review of published literature and meta-analysis of clinical trials of acute spinal cord injury treatment with high-dose steroids within eight hours of onset, the authors concluded that there is no benefit regarding neurological recovery and function and an increased risk of adverse side effects from gastrointestinal bleeding.

SOURCE: Liu Z, Yang Y, He L, et al. High-dose methylprednisolone for acute traumatic spinal cord injury. *Neurology* 2019;93:e841-e850.

Acute traumatic spinal cord injury (SCI) affects nearly half a million people every year globally, with the majority of patients being severely disabled. Given very few therapeutic options to improve outcomes after SCI, the use of high-dose steroids has been revisited. The authors of a landmark trial, the National Acute Spinal Cord Injury Study (NASCIS-2), showed that methylprednisolone did not result in improvement in functional recovery or mortality after SCI compared to placebo. However, prespecified post-hoc analyses suggested a modest benefit for recovery of motor and sensory function when methylprednisolone was administered within eight hours of injury. Large observational studies since then have failed to demonstrate improved outcomes after SCI with steroids. As a result, major guidelines either equivocate or recommend avoiding steroids in these patients. However, a recent guideline update has suggested a 24-hour infusion of high-dose methylprednisolone within eight hours of SCI, which has become a point of contention among clinicians.

In this study published in *Neurology*, Liu et al presented a systematic review and meta-analysis of published literature restricted to the use of high-dose steroids within eight hours of SCI. A total of 16 studies, including three randomized trials, were included. The main outcomes were motor and sensory recovery, incident adverse events, and cost of hospitalization. The authors concluded that there was no significant difference in motor or sensory recovery scores among SCI patients, regardless of steroid use. Furthermore, similar results were obtained when stratified by duration of follow-up. However, the use of high-dose methylprednisolone was

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Neurology [ALERT]

Stroke Alert

By Matthew E. Fink, MD

Intravenous Thrombolysis Prior to Mechanical Thrombectomy Improves Outcome

SOURCE: Katsanos AH, Malhotra K, Goyal N, et al. Intravenous thrombolysis prior to mechanical thrombectomy in large vessel occlusions. *Ann Neurol* 2019;86:395-406.

Since 2015, with the publication of five separate clinical trials demonstrating the benefit of mechanical thrombectomy, the standard of care for patients with large vessel occlusion (LVO) has been thrombectomy. There have been debates regarding the role of intravenous thrombolysis in LVO patients, with arguments that 1) it is better to treat all patients with intravenous thrombolysis regardless of whether they are candidates for mechanical thrombectomy, or 2) an LVO patient should go to directly to thrombectomy as soon as possible and skip the time it takes to administer intravenous thrombolytics. Underlying this argument is the fact that our ability to identify and diagnose patients with an LVO is far from perfect, and many such patients are found to have small vessel occlusion or distal occlusions that are not amenable to thrombectomy. Depriving a patient of thrombolysis deprives that person the opportunity to benefit from that treatment.

The authors of this study investigated the comparable safety and efficacy of bridging therapy with intravenous thrombolysis compared to direct mechanical thrombectomy in patients with acute ischemic stroke. They reviewed all available observational studies and analyses from randomized controlled trials that provided data on outcomes in patients stratified by intravenous thrombolysis treatment prior to mechanical thrombectomy. They identified 38 observational studies, resulting in evaluation of 11,790 LVO patients, of whom 56% were treated with bridging thrombolysis.

Compared to the patients treated with direct mechanical thrombectomy, bridging thrombolysis was associated with a higher likelihood of functional independence after three months (odds ratio [OR], 1.52), better functional improvement at three months as measured by a one-point decrease in the modified Rankin scale score (OR, 1.52), better early neurological improvement (OR, 1.21), successful recanalization (OR, 1.22), and successful recanalization with two or fewer device passes (OR, 2.28). Bridging therapy also was related to a lower likelihood of death at three months (OR, 0.64). The two groups did not differ significantly in the rate of symptomatic intracranial hemorrhage.

Bridging therapy with intravenous thrombolysis appears to be associated with improved functional outcome without any additional complications compared to direct mechanical thrombectomy for patients with acute ischemic stroke who have LVOs. ■

Continued from page 15

associated with an increased risk of gastrointestinal hemorrhage and respiratory infections. Finally, there was no cost-benefit to using steroids after SCI.

■ COMMENTARY

These study investigators summarized the current evidence on use of high-dose steroids after SCI. Given the lack of improvement in functional status with administration of high-dose steroids, coupled with a higher risk of steroid-related complications, the risk-benefit profile would favor avoiding steroids after SCI. Recent AOSpine guidelines[1] advocating high-dose methylprednisolone for 24 hours were based on a meta-analysis, albeit a less comprehensive one that had rigid inclusion criteria compared to the current study. That said, one of the limitations of the current study is the significant heterogeneity between individual studies and the lack of a meta-regression to identify potential sources of heterogeneity. The overwhelming futility of steroids in SCI observed in multiple observational studies and two randomized trials likely will impact the feasibility of future clinical trials on the use of methylprednisolone in the first eight hours after injury. Comprehensive meta-analyses such as the current study may lend support to prevent harm by avoiding steroids in patients with SCI. ■

REFERENCE

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CME QUESTIONS

1. **In the study by Tomson et al, which of the following major congenital malformations increased during the 14-year analysis period?**
   a. Cardiac
   b. Cleft palate
   c. Renal
   d. Neural tube
2. **Which of the following statements regarding chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is true?**
   a. CIDP patients with recent antecedent respiratory infection more often have CIDP with acute onset or cranial nerve involvement.
   b. Diets that exclude rice are associated with lower risk of CIDP.
   c. Eating fish increases CIDP risk.
   d. Fruit, cheese, and eggs protect against CIDP.
3. **In the RUN DMC study investigating the association between adiposity and vascular cognitive impairment, which is true?**
   a. Higher adiposity measures have a detrimental effect on cerebral small vessel disease markers in both men and women.
   b. Higher adiposity measures were associated with lower brain volumes in women but not men.
   c. Baseline adiposity measures were associated with dementia at follow-up in both men and women.
   d. Survival bias may have influenced the outcomes from the study.
4. **Intravenous thrombolysis should be administered to all patients with acute ischemic stroke who present within 4.5 hours of onset, regardless of eligibility for mechanical thrombectomy, if there are no contraindications.**
   a. True
   b. False

CME OBJECTIVES

Upon completion of this educational activity, participants should be able to:

- discuss current scientific data regarding the diagnosis and treatment of neurological disease;
- discuss the pathogenesis and treatment of pain;
- describe the basic science of brain function;
- discuss new information regarding new drugs for commonly diagnosed neurological conditions and new uses for traditional drugs;
- identify nonclinical issues of importance for the neurologist.

[IN FUTURE ISSUES]

Headaches and Migraines