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Neurology [ALERT®]

Evidence-based summaries of the latest clinical neurology research

ABSTRACT & COMMENTARY

Taste, Smell, and the Insular Cortex

By Steven Karceski, MD

Assistant Professor of Clinical Neurology, Department of Neurology, Weill Cornell Medical College

Dr. Karceski reports he provides patient education for NeuroPace and Cyberonics.

SYNOPSIS: Olfaction and taste appear to be localized in the insular cortex with bilateral representation.

SOURCE: Mazzola L, Royet JP, Catenoix H, et al. Gustatory and olfactory responses to stimulation of the human insula. *Ann Neurol* 2017; Aug 10. doi: 10.1002/ana.25010. [Epub ahead of print].

Very specific regions of our brains process the sensations of taste and smell. Animal studies, neuroimaging, metabolic studies (such as PET), and an analysis of cerebral lesions in humans have shown that these sensations are processed bilaterally in the parietofrontal operculum and insula. However, there has been some debate as to which part of the insula is responsible for this important brain function. There are many reasons for this, including the fact that it is very difficult to test one of these sensations without activating another. For instance, noxious stimuli also will activate the trigeminal pathways. A small amount of liquid that is placed in the mouth will go into the nasopharynx, stimulating smell. Direct cortical stimulation eliminates these confounding factors and is likely to be a much more accurate way of identifying the regions of the brain responsible for processing the sensations of taste and smell. Mazzola et al, working at the University Hospital of Saint-Etienne (France), reported their observations of taste and smell sensations using direct electrical stimulation of the insular cortex.

The investigators stimulated the human brain, using stereotactically placed electrodes, which had been placed as part of an evaluation for epilepsy surgery and had two main functions. First, they were used to identify the region of seizure onset in these patients in preparation for surgical removal of the seizure-causing zone. Second, the electrodes were used to stimulate the cortex, thereby identifying regions of eloquent cortex that would need to be spared during the epilepsy surgery.

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[INSIDE]

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Mazzola et al identified 221 patients who had insular cortex stimulation at the University Hospital between March 1997 and January 2015. All were undergoing an evaluation for epilepsy surgery. Confirmation of electrode placement occurred by either MRI (after 2009) or by superimposing a radiograph over the patient's MRI images. The study included 107 women and 114 men, with an average age of 35 years. The investigators used a standard method of cortical stimulation (50 Hz square-wave impulses, pulse duration 0.5 milliseconds, train duration < 5 seconds, intensity 0.2 mA to 3.5 mA). There were 651 electrical stimulations of the insular cortex in this group of patients, and 550 produced a clinical response. The most frequent responses, which occurred in 61% of the stimuli, were somatosensory (pain, thermal sensations, non-painful somatic sensations). Auditory responses occurred in 8%, followed by vestibular in 7%. The taste and smell responses were infrequent, accounting for 2.7% and 1.1%, respectively.

Both the taste and smell responses occurred when stimulating areas in the middorsal region of the insula. The taste (gustatory) responses occurred in both hemispheres equally (3.0% on the right; 2.6% left). Most of the subjective taste sensations were unpleasant. Most people could not identify the taste, just that is was "nasty," "acidic," "metallic," or "salty." The smells also occurred when stimulating either hemisphere, and were most often described as "metallic" or "chlorine." Many patients had trouble identifying whether the sensation was a taste or a smell. Interestingly, the location of cortical stimulation for taste and smell overlapped.

■ COMMENTARY

It has long been observed that smell, taste, and oropharyngeal sensation are closely associated brain functions. By stimulating various regions of the human insula, Mazzola et al showed that these sensory modalities were closely related to each other anatomically. In fact, they further demonstrated that taste and smell are brain functions that *overlap* in the insula. Although we think of taste and smell as separate senses, this observation may explain why it is often difficult to distinguish one from the other. Further, oropharyngeal sensations and unusual or unpleasant tastes and smells often are part of a person's seizure semiology. When patients report these sensations during their seizures, Mazzola's study results indicated that the insula should be considered as a place where the seizure has started or to which it has propagated. ■

ABSTRACT & COMMENTARY

Tau as a Biomarker of Acute and Chronic Traumatic Brain Injury

By Halinder S. Mangat, MD

Assistant Professor of Neurology, Weill Cornell Medical College

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

SYNOPSIS: The ongoing search for reliable biomarkers of traumatic brain injury repeatedly has demonstrated the reliability of using plasma phosphor-tau levels to help distinguish injury from normal, and severe injury from mild injury.

SOURCE: Rubenstein R, Chang B, Yue JK, et al. Comparing plasma phosphor tau, total tau, and phospho tau-total tau ratio as acute and chronic traumatic brain injury biomarkers. *JAMA Neurol* 2017; Jul 24. doi: 10.1001/jamaneurol.2017.0655. [Epub ahead of print].

The TRACK-TBI investigators explored the measurement of plasma tau as a total protein, phosphorylated protein, and the ratio between the two as a correlate of acute and chronic traumatic brain injury (TBI).[1] In this study, 196 patients with acute TBI and 21 patients with chronic TBI were enrolled and blood samples were compared with assays from 20 commercially acquired, healthy control samples with no history of TBI. Patients were predominantly male (74%), white (83%)

with mild head injury (81% Glasgow Coma Scale [GCS] score 13-15; 3% GCS score 9-12; 6% GCS score < 9), and half had normal CT (55%). Patients with acute TBI had blood collected within 24 hours of injury, and chronic TBI patients had blood collected at an average of 176 days. The investigators developed and used a new high-sensitivity assay: multi-arrayed fiberoptics conjugated with rolling circle amplification (a-EIMAF), which previously has been validated.

Higher hypophosphorylated tau protein (P-tau) and P-tau and total-tau (P-tau-T-tau) ratios both significantly were correlated with abnormal CTs, TBI severity by GCS (13-15, 9-12, 3-8), and CT Marshall score, and were significantly higher in TBI patients than in controls. In addition, both indices could distinguish mild TBI from controls as well as moderate and severe TBI. Analyses of area under the curve (AUC) were 0.9-1.0 for the two indices in discrimination between all acute TBI and healthy controls, 0.7-0.8 in distinguishing between mild and moderate/severe TBI, and 0.9-1.0 in distinguishing patients with normal vs. abnormal CT scans. The two indices also correlated with good outcomes, being inversely proportional, but had poor discrimination by AUC; the latter was significantly better (0.7-0.8) for poor outcome (Glasgow Outcome Scale-Extended < 5). Lastly, and surprisingly, P-tau and P-tau-T-tau ratio both were significantly higher in chronic TBI patients with AUC 0.9-1.0.

■ COMMENTARY

This study joins a few other outstanding studies exploring reliable and robust blood biomarkers of TBI. The clinical field of TBI, especially acute TBI, has remained at a standstill in terms of improved identification of patients. For several decades, the GCS scale has been used to classify severity, and in the last few decades, CT has been used to identify and classify TBI. Patients with mild TBI who do not have sustained impairment in consciousness frequently have no findings on CT examination. Yet they form up to 80% of the TBI burden. This has been highlighted only recently and brought to the public domain by increased press of sequelae of mild TBI from sports and blast injury in war.[2-4] Therefore, development of biomarkers is the pressing need of the hour.

The choice of the protein is appropriate given that tau is a scaffolding axonal microtubule protein whose abnormal posttranslational transformation by hyperphosphorylation and accumulation has been known to play a role in long-term brain injury, as seen in chronic traumatic encephalopathy and Alzheimer's disease. The consistent association of P-tau and the P-tau-T-tau ratio with clinical condition, lesion on CT, and ability to differentiate mild TBI from more severe TBI makes this study's results exciting.

A few drawbacks of the study, as stated by the authors, are that the samples from controls and patients were handled differently, and control samples were few and commercially obtained. In the future, the study investigators are validating the assay prospectively using patient family or friends as controls.

[The clinical field of traumatic brain injury (TBI), especially acute TBI, has remained at a standstill in terms of improved identification of patients. … development of biomarkers is the pressing need of the hour.]

However, an extensive network as TRACK-TBI should perhaps look to concomitantly study other biomarkers that have shown recent promise, such as GFAP (with breakdown products),[5] ubiquitin C-terminal hydrolase L1,[6] and brain-derived neurotrophic factor,[7] to validate not only which biomarker provides the highest accuracy and reliability, but also which is most efficient and cost-effective. ■

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ABSTRACT & COMMENTARY

REM Sleep, Not Slow-wave Sleep, Decreases Dementia Risk

By Alan Z. Segal, MD

Associate Professor of Clinical Neurology, Weill Cornell Medical College

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

SYNOPSIS: In a series of clinical studies of cognitively normal people older than 60 years of age, disruption of REM sleep and reduced quantity of REM sleep increased the risk of developing Alzheimer-type dementia.

SOURCE: Pase MP, Himali JJ, Grima NA, et al. Sleep architecture and the risk of incident dementia in the community. *Neurology* 2017; Aug. 23. pii: 10.1212/WNL.0000000000004373. doi: 10.1212/WNL.0000000000004373. [Epub ahead of print].

In last month's *Neurology Alert*, we reviewed a landmark study in the journal *Brain*, showing that disruption of slow-wave sleep led to increases in cerebrospinal fluid amyloid-β levels. The implication was that this deep phase of non-REM sleep plays a unique role in cleansing the brain of toxic substances that otherwise would promote the development of dementia. No relationship between REM sleep and amyloid was found.

The current study, published on the heels of the *Brain* report, has nearly opposite findings. Polysomnography was performed in 321 subjects from the Framingham offspring study who were older than 60 years of age at the time of sleep assessment. In 12 years of follow-up, 32 cases of incident dementia (primarily Alzheimer's type) were recorded — the majority of these during the latter stages of follow-up. For each percentage reduction in the quantity of REM sleep, there was a 9% increased risk of dementia. Four times as many subjects in the lowest quartile of REM duration developed dementia when compared to subjects in the highest quartile of REM sleep. In direct contradiction to the *Brain* report, there was no relationship found between slow-wave sleep and incident dementia. Furthermore, REM loss was not thought merely to be a marker of mental decline, since any patient with mild cognitive impairment or dementia onset within the first three years of follow-up was excluded.

■ COMMENTARY

Although REM sleep may play a role in promoting synaptic plasticity and the consolidation of memories, it remains speculative as to how REM sleep may protect against dementia. Although there is muscular relaxation during REM, the activity of the cortex more closely approximates the waking state, in contrast to the downregulation of brain activity observed in slow-wave sleep. Despite the apparent contradictions in these two important studies, there is little doubt that sleep in general, whether slow-wave or REM, plays a crucial homeostatic role, not only in our daily function but also in our long-term brain health. It is important to maintain good sleep habits with advancing age to reduce the risk of developing Alzheimer's disease and other dementias. ■

ABSTRACT & COMMENTARY

Lamotrigine for Myotonia

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: In a randomized, double-blind, placebo-controlled treatment trial of patients with non-dystrophic myotonia, those treated with lamotrigine experienced significant improvement.

SOURCE: Andersen G, Hedermann G, Witting N, et al. The antimyotonic effect of lamotrigine in non-dystrophic myotonias: A double-blind randomized study. *Brain* 2017;140:2295-2305.

Myotonia causes troublesome and disabling symptoms in patients with the non-dystrophic myotonias: myotonia congenita and paramyotonia congenita. Several medications may be offered to treat the resultant muscle stiffness and pain, including carbamazepine, phenytoin, procainamide, propafenone, and flecainide, whereas quinine and procainamide are no longer recommended because of adverse effects

on cardiac conduction. However, only mexiletine has been shown in double-blind, randomized clinical trials to be superior to placebo, to be well-tolerated, and without cardiac conduction or other serious side effects. However, it is expensive, not widely available because it is manufactured only in Mumbai, and patients often decline it because of common reactions including dizziness, tremor, insomnia, diarrhea, and headache. Lamotrigine, a sodium-channel blocker like mexiletine, may be an excellent alternative.

Between November 2013 and July 2015, the departments of Neurology, Neuromuscular Centers, of the Universities of Copenhagen and Aarhus, Denmark, conducted a Phase II, randomized, double-blind, placebo-controlled, crossover study in which patients received eight weeks of lamotrigine followed by a one-week washout period, and then eight weeks of placebo, or vice versa. Doses were escalated every other week, beginning at 25 mg, and increasing to 50 mg, 150 mg, and 300 mg. Primary and secondary outcome measures, performed at zero, six, and eight weeks, encompassed, respectively, the Myotonic Behavior Scale (MBS), and four functional timed tests assessing eye and hand closure relaxation times and leg myotonia using the Timed Up and Go (TUG) test and the 14 Step Stair Test (14SST). Statistical analysis included the Mann-Whitney and paired t-tests, the paired two-tailed t-test, or Wilcoxon signed rank test as appropriate, and the McNemar test, with a P value < 0.05 considered significant.

Among 26 patients (ages 19 to 74 years) enrolled, 22 completed the study and four dropped out because of illness. Lamotrigine-treated patients experienced a significant improvement in MBS, the primary outcome measure, as well as significant improvement in all four timed tests, the secondary outcome measures. Placebo had no effect on any of the outcome measures. Fifteen patients experienced side effects, most commonly headache, fatigue, muscle or joint pain, skin rash, sore throat, and nausea; two of the 15 patients were excluded from receiving further medication because of an allergic reaction in one patient and a bleeding bacterial ulcer in the other. Lamotrigine appears effective and safe, is widely available, and is less costly, and should be offered as first-line treatment for myotonia in non-dystrophic myotonia patients.

■ COMMENTARY

Approved in 1991 and a mainstay antiepileptic agent for focal and generalized tonic-clonic seizures ever since, lamotrigine also is beneficial in absence epilepsy and Lennox-Gastaut syndrome and is further licensed for the treatment of bipolar disorder. It may be given once or twice daily, has 95-100% absorption bioavailability with a half-life of 22 to 36 hours, and should be introduced slowly to reduce the risk of an allergic reaction. In addition to blocking the fast inactivation state of sodium channels, which may be its mechanism of action in myotonia, it also inhibits N-type and P-type high-voltage activated calcium currents, as well as enhancing potassium repolarizing currents. Centrally, it decreases the excitability of pyramidal neuron dendrites by acting directly on the hyperpolarization-activated calcium current. Insomnia is its one unusual, and often forgotten, adverse effect, not occurring with any other sodium channel blocker. ■

ABSTRACT & COMMENTARY

Polyneuropathy and Nutrition

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: Other than the identification of a specific vitamin or essential element deficiency, overall nutritional status does not appear to play any role in the development of idiopathic neuropathies in adults.

SOURCE: Visser NA, Notermans NC, de Vries JHM, et al. The role of nutrition as risk factor for polyneuropathy: A case-control study. *J Peripher Nerv Syst* 2017; Aug 8. doi: 10.1111/jns.12233. [Epub ahead of print].

Despite in-depth evaluations, a cause is never determined in about 33% of patients with polyneuropathy. Most such patients are older than 50 years of age; usually present with the insidious onset of slowly progressive sensory symptoms including tingling, numbness, burning, or aching discomfort, generally with preserved strength; and often demonstrate an axonal polyneuropathy on electrodiagnostic studies. Implicated, but unproven, are multiple etiologies including abdominal obesity, hypertension, lipid abnormalities, glucose intolerance, or oxidative stress. Visser et al addressed the question regarding polyneuropathy — variously referred to as chronic idiopathic axonal polyneuropathy (CIAP), chronic sensory polyneuropathy, chronic polyneuropathy of undetermined cause, chronic idiopathic polyneuropathy of the elderly, and unclassified peripheral neuropathy — Is nutrition a risk factor for developing polyneuropathy?

The study included all patients referred to the Department of Neurology, University Medical Center Utrecht Neuromuscular Outpatient Unit in The Netherlands, and diagnosed with CIAP between Oct. 1, 2008, and July 1, 2012. Controls for the study were healthy individuals participating in a prospective, population-based amyotrophic lateral sclerosis study in The Netherlands. Patients were excluded if they had a history of diabetes or consumed ≥ 10 g/day of alcohol. All patients underwent a standardized clinical evaluation for polyneuropathy, including history and physical examination, laboratory studies encompassing vitamin levels, lipid profile, celiac serologic screening, nerve conduction studies, and, where indicated, genetic testing, lumbar puncture, chest radiograph, and magnetic resonance imaging. To address nutritional factors, a validated 199-item food frequency questionnaire was completed by patients and controls, covering their intake over the prior month. Enrollees were contacted by phone, where necessary, to supply missing data or clarify inconsistencies. Statistical analyses comprised chi-square testing, Student's t-test, Mann-Whitney U test, and multivariate binary logistic regression analysis, applying the Benjamini-Hochberg procedure, where necessary, to adjust uncorrected *P* values.

Among 318 CIAP patients and 636 controls, the mean age of onset was 59.1 years, with 73% demonstrating sensory CIAP and 27% having sensorimotor CIAP. No association with CIAP risk was found with respect to the intake of 28 different nutrients, including carbohydrates, protein, fat, fiber, vitamins, minerals, glutamate, or phytoestrogens, regardless of moderate alcohol intake. Patients with CIAP who drank alcohol had a lower intake of vitamin B2 (riboflavin) and carbohydrates, compared to those with CIAP who did not drink, but B2 levels were not measured and thus its role in the etiology of polyneuropathy could not be addressed. Overall, no difference was found between the two groups regarding energy or nutrient intake, allowing for the conclusion that poor nutrition does not appear to be a risk factor for CIAP.

■ COMMENTARY

These investigators examined nutrition in otherwise normal persons and found that it played no role in the development of CIAP. However, multiple nutritional deficiencies likely play a central role in the development of neuropathy in patients with a history of alcohol abuse, bariatric surgery, gastrectomy, and anorexia. Both acute and chronic neuropathies have been described in these instances, and nutritional deficiency must be considered in their differential diagnosis, which also includes immune, toxic, infectious, and metabolic etiologies. Appropriate measurements of these various nutrients in the blood should be undertaken before any vitamin or nutritional supplements are prescribed. ■

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Stroke Alert

By Matthew E. Fink, MD

Sudden Prehospital Death From Subarachnoid Hemorrhage

SOURCE: Lindbohm JV, Kaprio J, Jousilahti P, et al. Risk factors of sudden death from subarachnoid hemorrhage. *Stroke* 2017;48:2399-2404.

Based on recent nationwide data reported from Finland, one-fourth of those experiencing their first ever subarachnoid hemorrhage (SAH) died suddenly before being admitted to a hospital. Most epidemiological studies have been based on hospitalized patients, and in prospective, long-term studies, the significant risk factors for SAH have included smoking, high blood pressure, female gender, and increasing age. However, risk factors that result in early sudden death have not been analyzed systematically. In this study from Finland, a cohort of 65,521 individuals was followed for up to 1.5 million person-years, and Cox proportional hazards were used to calculate hazard ratios for all SAH risk factors, as well as socioeconomic status. A risk model analyzed differences in risk factors between hospitalized patients with SAH and those who had sudden prehospital death from SAH (autopsy proved).

From this cohort, the investigators identified 98 sudden-death SAH patients and 445 hospitalized SAH patients. Increased consumption of cigarettes of > 5 per day elevated sudden death SAH risk (hazard ratio [HR], 1.28) more than hospitalized SAH. A higher systolic blood pressure also was a risk factor for sudden death from SAH (HR, 1.34). Study patients living alone were at elevated risk for sudden death from SAH (HR, 2.09). There were no incidents of sudden death from SAH patients who were known to be normotensive, never smoked, and were younger than 50 years of age. Sudden death from SAH appears to be highest among those with the most adverse risk factor profile and those who lived alone. Younger patients, under the age of 50, who had normal blood pressure and had never smoked, had a low risk for sudden death from SAH. ■

Idarucizumab for Reversal of the Anticoagulant Effects of Dabigatran

SOURCE: Pollack CV, Reilly PA, van Ryn J, et al. Idarucizumab for dabigatran reversal – full cohort analysis. *N Engl J Med* 2017;377:431-441.

Orally administered direct thrombin inhibitors, as well as Factor Xa inhibitors, have become important additions as anticoagulants to stroke prevention therapies in patients with atrial fibrillation. However, one of the major drawbacks has been the inability to reverse the antithrombotic effects during a bleeding emergency, such as trauma or intracranial hemorrhage. Prothrombin complex concentrate is recommended in guidelines to reverse the effects of these agents, but this treatment has never been proven to be effective. Dabigatran, a direct thrombin inhibitor, was the first new oral antithrombotic to be approved by the FDA, and is now the first to have an effective antidote for reversal of its antithrombotic effects. Pollack et al reported the details of the full cohort analysis of the use of the monoclonal antibody, idarucizumab, for reversal of this antithrombotic medication. This trial was a multicenter, prospective, open-label study to determine whether 5 mg of intravenous idarucizumab could reverse the anticoagulant effects of dabigatran in patients who had uncontrolled bleeding (Group A) or were about to undergo an urgent surgical procedure (Group B). The primary endpoint was the percentage reversal of the anticoagulant effects within four hours of administration of idarucizumab, on the basis of a dilute thrombin time or ecarin clotting time. Secondary endpoints were restoration of hemostasis and safety outcomes.

A total of 503 patients were enrolled in the study: 301 in Group A and 202 in Group B. The median percentage reversal of dabigatran was 100%. In Group A, 137 patients (45.5%) presented with gastrointestinal bleeding and 98 (32.6%) presented with intracranial hemorrhage. Median time to cessation of bleeding was 2.5 hours. In group B, the median time to initiation of the surgical procedure was 1.6 hours, and periprocedure hemostasis was normal in 93.4% of the patients. At 90 days of follow-up, thrombotic events occurred in 6.3% of patients in Group A and 7.4% in Group B. Ninety-day mortality was 18.8% and 18.9%, respectively. The mortality was attributed to the complex multi-organ failure that occurred in many of these critically ill patients. No serious adverse safety signals emerged related to the administration of this monoclonal antibody. In conclusion, the administration of idarucizumab is effective and safe for the reversal of the direct thrombin inhibitor, dabigatran, and should be used in appropriate clinical situations. ■

What Is the Ideal Target for Blood Pressure Control?

SOURCE: Berlowitz DR, Foy CG, Kazis LE, et al. Effects of intensive blood pressure treatment on patient reported outcomes. *N Engl J Med* 2017;377:733-744.

The Systolic Blood Pressure Intervention Trial (SPRINT; *N Engl J Med* 2015;373:2103) showed that among older adults with hypertension and a high risk of cardiovascular disease, blood pressure treatment that targeted a systolic blood pressure of < 120 mmHg (intensive treatment) led to lower rates of cardiovascular events and death than treatment that targeted a systolic blood pressure of < 140 mmHg (standard treatment). This recommendation was controversial, and there was great concern that adoption of the lower blood pressure target into general clinical practice might be limited by concerns regarding its effect on patient-reported outcomes, such as health status, quality of life, and satisfaction with care. In addition, reductions in cerebral blood flow, especially among older patients who have physical and cognitive impairments, might lead to lightheadedness, confusion, and falls with injury. Therefore, a study that looked at quality-of-life outcomes was organized to address these issues.

Berlowitz et al randomly assigned 9,361 participants with hypertension to a systolic blood pressure target of < 120 mmHg or a target of < 140 mmHg. Patient-reported outcomes included scores on the Physical Component Summary and Mental Component Summary of the Veterans RAND 12-item Health Survey, as well as a patient health questionnaire, which included items for depression, patient-reported satisfaction with care and blood pressure medications, and adherence to blood pressure medication prescriptions. Patients in the intensive treatment arm received an average of one additional antihypertensive medication and their median systolic blood pressure was 14.8 mmHg lower than the group that received standard care. There were no significant differences in the scores reported by patients regarding quality of life, depression, or patient-reported satisfaction scores. There were no significant differences regarding physical or cognitive function. Satisfaction with blood pressure care and medications was high in both treatment groups, and there were no significant differences in adherence to blood pressure medication prescriptions. In conclusion, the patient-reported outcomes in those who received intensive treatment with a target systolic blood pressure of < 120 mmHg were similar to those who received standard care, supporting the recommendations of SPRINT. ■

Cerebrolysin Is Unproven as a Neuroprotectant for Acute Ischemic Stroke

SOURCES: Ziganshina LE, Abakumova, Vernay L. Cerebrolysin for acute ischemic stroke – Cochrane Corner. *Stroke* 2017;48:e245-e246.

Bereczki D. Hope dies last – Evidence again fails to support a neuroprotectant: Cerebrolysin for acute ischemic stroke. *Stroke* 2017;48:2343-2344.

A personal note: I have directed a neurology symposium in Salzburg, Austria, for the past 10 years, and it is attended each year by 30 to 40 neurologists from Eastern Europe and Asia. Every year, as I discuss stroke treatment, the participants bring up the use of Cerebrolysin, which is approved as standard therapy in many Eastern European and Asian countries. The question is always, "Why don't you use Cerebrolysin in the United States?"

Cerebrolysin is a mixture of low molecular weight peptides and amino acids derived from pig's brain, and has been used widely in the treatment of acute ischemic stroke in Russia, Eastern Europe, China, and other Asian countries. A

recent Cochrane Review based on six trials in the published literature concluded that the use of Cerebrolysin has no effect on fatality. In addition, none of the trials demonstrated improvements in neurological or functional outcome, including a recent trial from China, as well as a large trial of 1,000 patients in Asia. None of the trials reported have shown any significant effect on death or disability, and the routine use of Cerebrolysin in acute stroke is not justified. ■

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CME QUESTIONS

1. **Which of the following statements is *true* regarding the brain localization of taste and smell?**
   a. Taste perception is localized in the left parietal lobe.
   b. Olfaction is localized in the right temporal lobe.
   c. Taste and smell both have localization in insular cortex, bilaterally.
   d. Olfactory hallucinations before a seizure will localize the focus to left temporal lobe.
2. **Which of the following would help distinguish mild TBI from healthy patients?**
   a. Total plasma tau
   b. Plasma P-tau
   c. Plasma P-tau-T-tau ratio
   d. Both b and c
   e. All of the above
3. **Disruption and/or lack of sleep may be a risk factor for the development of Alzheimer's disease.**
   a. True
   b. False
4. **Which is a common side effect of lamotrigine?**
   a. Headache
   b. Fatigue
   c. Muscle or joint pain
   d. Skin rash
   e. All of the above
5. **Which of the following have been identified as central to the development of chronic idiopathic axonal polyneuropathy?**
   a. Decreased carbohydrate intake
   b. Decreased protein intake
   c. Decreased glutamate intake
   d. Decreased phytoestrogen intake
   e. None of the above
6. **Subarachnoid hemorrhage is a common cause of sudden death outside of the hospital.**
   a. True
   b. False
7. **Dabigatran, a direct thrombin inhibitor, is dangerous to use because it cannot be reversed in a bleeding emergency.**
   a. True
   b. False
8. **It is dangerous to lower systolic blood pressure to 120 mmHg when treating hypertension with medications.**
   a. True
   b. False

[IN FUTURE ISSUES]

Update on Neuro-oncology