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INSIDE

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Special Update: Stroke Alert

Endovascular Therapy for Acute Stroke Still of Unproven Benefit: The Quest Continues

ABSTRACT & COMMENTARY

By Dana Leifer, MD

Associate Professor of Clinical Neurology, Weill Cornell Medical College

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

Synopsis: *CT and MRI parameters were identified that appeared to predict final infarct volume and clinical outcome of acute stroke patients. The parameters were used to develop a model to identify patients most likely to benefit from acute treatment with endovascular arterial therapies. However, several very recent trials, reported at the 2013 International Stroke Conference, failed to find benefit for endovascular treatment using this model and other protocols.*

Source: Kidwell C, et al. Multiparametric MRI and CT models of infarct core and favorable penumbral imaging patterns in acute ischemic stroke. *Stroke* 2013;44:73-79.

INTRAVENOUS (IV) OR INTRA-ARTERIAL TREATMENT WITH TISSUE PLASMINOGEN activator (tPA) and mechanical clot extraction can limit the damage that some ischemic strokes cause, but they also can cause complications, including hemorrhage into established infarcts. The length of the interval between the time when a patient was last known to be normal and the time of treatment is currently a key factor in patient selection, but a more reliable way to identify patients who would benefit from treatment is needed, especially for endovascular procedures. Some patients, within a given time window, have completed infarcts while others outside of the window may have a large penumbra — an area of ischemic tissue that is not infarcted and that potentially could be salvaged.

To identify imaging parameters predicting response to therapy, Kidwell and colleagues studied acute stroke patients with intracranial occlusions of large arteries in the anterior circulation on CT or MR angiography. Prior to

treatment, the patients also underwent CT perfusion scans or MRI with diffusion and perfusion-weighted imaging to identify regions of infarction and of salvageable ischemia. Follow-up imaging was performed to define the final infarct. The investigators derived models to predict the fate of individual voxels and combined these to generate estimates of final infarct volume and to predict the clinical outcome. Good outcome was defined as a modified Rankin Scale of 2 or less.

The MRI model predicted infarction at the voxel level with 71% accuracy and the CT model with 79% accuracy. Analysis of the models suggested the optimum cutoff points for predicting good clinical outcomes were an infarct volume of < 90 mL and a ratio of predicted infarct to tissue at risk of < 0.7. Using these cutoffs, the MRI model predicted good outcomes with 85% accuracy and the CT model with 78% accuracy in the cohorts used to derive the model.

Kidwell and colleagues then tested these models in the Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy (MR RESCUE) study. They presented the results recently at the International Stroke Conference (ISC), where two other randomized trials of endovascular treatment of acute stroke also were presented.

MR RESCUE enrolled patients with intracranial internal carotid or middle cerebral artery occlusions who could undergo CT perfusion imaging or MRI and be treated by embolectomy within 8 hours from the time when they were last known normal. Patients who were eligible for IV tPA were treated with it prior to enrollment and underwent imaging to look for a penumbra after completion of the IV tPA.

■ COMMENTARY

Despite the promising imaging results that provided the foundation for the trial as discussed above, MR RESCUE failed to show any benefit for mechanical embolectomy over medical management even in patients with a large penumbra. Patients with a penumbra did better than those without one whether treated medically or by mechanical embolectomy. One possible explanation is that embolectomy was done relatively late with a mean time of 6.4 hours from when patients were last known to be normal to the start of endovascular procedures.

The Interventional Management of Stroke-III (IMS-III) trial, which was also just reported at the ISC, treated patients more quickly. Endovascular procedures were completed in an average of 5.4 hours from the time patients were last known to be normal. Nevertheless, IMS-III still found no overall benefit for combined IV tPA and endovascular treatment compared to IV tPA alone. Secondary analysis, however, showed that there was a trend toward benefit from endovascular treatment if IV tPA was started within 2 hours and if the time from starting IV tPA to groin puncture was < 90 minutes. In addition, there was an estimated 14% relative risk reduction per 30-minute decrease in time to completion of the endovascular procedure, so faster treatment may make a difference.

The Local versus Systemic Thrombolysis for Acute Ischemic Stroke (SYNTHESIS Expansion) study, also just reported at the ISC, did not find an overall difference between combined IV tPA and endovascular treatment vs IV tPA treatment alone, even though endovascular treatment was begun a median of only 3.75 hours from stroke onset — only 1 hour later than the median time for starting IV tPA in the study.

Taken together, the results of these three newly reported studies suggest that very rapid treatment will be needed to demonstrate a significant benefit from endovascular treatment. In view of these results and nonrandomized experience suggesting dramatic benefits for some patients from embolectomy, additional randomized studies are needed with newer devices such as stent retrievers that can open arteries more quickly and with higher success rates than the devices used in the trials that were just reported. ■

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Please call **Leslie Coplin**, Executive Editor, at leslie.coplin@ahcmedia.com.

A Newly Discovered Genetic Cause of Alzheimer's Disease – Mutations of TREM2

ABSTRACT & COMMENTARY

By Michael Lin, MD, PhD

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

Synopsis: *Genome sequencing and analysis of mutations of the TREM2 gene demonstrated that homozygotes have an increased risk of developing Alzheimer's disease, and carriers have cognitive impairments compared to age-matched controls.*

Sources: Jonsson T, et al. Variant of TREM2 associated with the risk of Alzheimer's disease. *N Engl J Med* 2013;368:107-116.

Guerreiro R, et al. TREM2 varients in Alzeimer's disease. *N Engl J Med* 2013;368:117-127.

INFLAMMATION IS THOUGHT TO PLAY A ROLE IN ALZHEIMER'S disease (AD) pathogenesis. Evidence of inflammation is seen in AD brains, including activated microglia, cytokines, and complement components. Providing further evidence for the role of inflammation, two recent studies presented back-to-back in the *New England Journal of Medicine* showed that a rare variant in TREM2 (triggering receptor expressed on myeloid cells 2) is associated with 3- to 5-fold increased risk of AD.

In the study by Jonsson et al, all the protein-changing mutations identified in whole genome sequence data from 2261 Icelanders were imputed in a case-control analysis of AD (3550 patients) and control patients. Other than ApoE and APP, the only marker that showed a significant genome-wide association with AD was a rare R47H missense mutation in TREM2 (odds ratio [OR], 2.92; 95% confidence interval [CI], 2.09-4.09; $P = 3.42 \times 10^{-10}$). The overall allele frequency for this mutation was 0.63% in Iceland. The association was replicated using datasets from the United States, Germany, the Netherlands, and Norway (combined OR, 2.83; CI, 1.45-5.40; $P = 0.002$). Finally, elderly carriers of the R47H TREM2 mutation without AD had poorer cognitive function than noncarriers ($P = 0.003$).

In the study by Guerreiro et al, there were significantly more mutations in TREM2 in 1092 AD cases than in 1107 controls. Of these mutations, the R47H mutation showed the strongest association with AD ($P < 0.001$). The association was replicated on meta-analysis of three imputed datasets of genome-wide association studies of AD ($P = 0.002$). The authors also directly genotyped the R47H variant in 1994 AD cases and 4062 controls, and again found a significant association with AD (OR, 5.05; 95% CI, 2.77-9.16; $P = 9.0 \times 10^{-9}$). TREM2 expression was increased in brains of transgenic APP mice compared to nontransgenic littermates.

■ **COMMENTARY**

Overall, the R47H mutation in TREM2 described in both papers is rare (allelic frequency < 1%), but the magnitude of risk conferred by the mutation (OR ~ 3-5) is similar to that conferred by the apoE4 allele. The pathogenesis of TREM2 in AD remains to be elucidated, but may provide some insight into AD pathogenesis in general. TREM2 is expressed in microglia, enhances phagocytosis (which may be relevant to clearance of amyloid), and promotes the "alternative activation" state of microglia, which is thought to be protective. TREM2 also suppresses proinflammatory cytokine signaling. Thus, loss of function of TREM2 could affect clearance of amyloid and promote inflammatory cascades.

Homozygous loss of function of TREM2 has previously been associated with early onset dementia and bone cysts with pathologic fractures, termed polycystic lipomembranous osteodysplasia with sclerosing leukoencephalopathy (Nasu-Hakola disease). It also has been associated with frontotemporal dementia with leukodystrophy. The papers above suggest that TREM2 is likely also associated with AD. ■

Autoantibodies to N-methyl-D-aspartate Receptor Found in Some Adults with Herpes Simplex Encephalitis: Are They Significant?

ABSTRACT & COMMENTARY

By Bianca D. Santomasso, MD, PhD, and Matthew E. Fink, MD

Dr. Santomasso is Chief Resident in Neurology, and Dr. Fink is Professor and Chairman, Department of Neurology, Weill Cornell Medical College

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

Synopsis: *Some patients with herpes simplex encephalitis develop autoantibodies against N-methyl-D-aspartate receptors. Sera from these patients cause a downregulation of neuronal synaptic markers in vitro, suggesting a potential pathogenic disease-modifying effect.*

Source: Pruss H, et al. N-methyl-D-aspartate receptor antibodies in herpes simplex encephalitis. *Ann Neurol* 2012;72:902-911.

Stroke Alert: A Review of Current Clinical Stroke Literature

By Matthew E. Fink, MD, *Professor and Chairman, Department of Neurology, Weill Cornell Medical College, and Neurologist-in-Chief, New York Presbyterian Hospital*

Special Report from the International Stroke Conference: Current Endovascular Interventions for Acute Ischemic Stroke Do Not Result in Better Clinical Outcomes than Intravenous Thrombolysis

Attendees of the international stroke meeting in Hawaii, in February 2013, were astonished by three reports of long-awaited trials comparing endovascular therapies with intravenous thrombolysis — IMS III,[1] SYNTHESIS,[2] and MR RESCUE.[3] In all three studies, the clinical outcomes were not statistically different between the intra-arterial interventional groups and the intravenous-medical groups.

In IMS III, the study was stopped, for futility, after 656 patients with moderate-to-severe ischemic stroke were randomized to either intravenous tPA alone or endovascular therapy after IV tPA. The primary outcome measure, a modified Rankin score of 2 or less at 90 days, did not differ significantly between the two groups (40.8% for endovascular and 38.7% with intravenous tPA), and there were no subgroups based on clinical severity that showed any differences in outcome. Mortality was similar between the groups (19.1% vs 21.6%) as was symptomatic intracerebral hemorrhage (6.2% vs 5.9%). The trial showed similar safety profiles and outcomes. Of note, there was variability in the devices used for endovascular therapy at the discretion of the operators — Merci retreiver, Penumbra system, Solitaire device, or intra-arterial tPA. Angiography had to begin within 5 hours of symptom onset and be completed within 7 hours.

In the SYNTHESIS trial, 362 patients with acute ischemic stroke were randomly assigned, within 4.5 hours of symptom onset, to intravenous thrombolysis with tPA or intra-arterial endovascular therapy using a combination of thrombolysis or clot retrieval, or both. The median time from stroke onset to start of treatment was 3.75 hours for endovascular therapy and 2.75 hours for intravenous tPA. The primary outcome was survival free of disability (Rankin score of 0 or 1) at 3 months, and there was no significant difference between the groups (30.4% for endovascular and 34.8% for intravenous). Odds ratios were adjusted for age, sex, stroke severity, and atrial fibrillation at baseline. Symptomatic intracranial hemorrhage occurred in 6% of each group and there were no significant differences in other serious adverse events or death rates.

The MR RESCUE trial used imaging in an attempt to select patients for treatment and predict outcome based on CT or MR measurements of potentially reversible ischemic penumbra. The study randomly assigned 118 eligible patients within 8 hours after onset of large-vessel, anterior-circulation ischemic strokes to undergo mechanical embolectomy with Merci retriever or Penumbra system, or receive standard care, which might include intravenous tPA. All patients underwent CT or MRI studies to determine infarct core and penumbra, and were stratified to favorable penumbra group or a non-penumbra pattern. For all patients, the mean time to enrollment was 5.5 hours, and 58% had a favorable

Herpes simplex virus encephalitis (HSE) is the most common cause of sporadic fatal viral encephalitis. Although the mortality and morbidity of HSE has been significantly reduced due to early antiviral therapy, even after treatment, about 35% of patients have severe neurological sequelae or even death. It is possible that not all symptoms of HSE result from a direct effect of viral invasion and neuronal cell lysis, but that a secondary autoimmune mechanism may be at play. This is suggested by three points that the authors mention: 1) combining acyclovir with corticosteroids may improve clinical outcome of HSE, 2) the disease course may be more severe in immunocompetent as compared to immunocompromised patients, and 3) some patients who experience clinical relapses of HSE after viral clearance are found to have proinflammatory profiles in their cerebrospinal fluid (CSF), suggesting that immunologically mediated pathogenicity may be at play.

In the current study, the authors set out to investigate the question of whether HSE patients might have pathogenic antibodies against neuronal cell antigens. They performed a blinded, retrospective analysis of 44 consecutive patients with polymerase chain reaction (PCR)-proven HSE, examining the serum and CSF for the presence of antineuronal antibodies by recombinant immunofluorescence or

penumbra pattern. Revascularization was successful in 67% of the embolectomy group. Mortality at 90 days was 21%, and the rate of symptomatic hemorrhage was 4%, without any significant differences between the two groups. Mean scores in the modified Rankin score did not differ between the groups, and there were no differences between the favorable penumbra pattern or the nonpenumbral pattern group. A favorable penumbra pattern did not predict a better outcome, and there was no difference between embolectomy vs standard care.

We congratulate the investigators of all three of these studies for their herculean efforts to complete this work, but we are disappointed by the results. How can we explain the findings, and what should be our next steps?

First, the methodology for clot extraction in all three studies used a first generation of devices, and the newer devices that are becoming available are technically superior at performing clot extraction. So, it is expected that use of these newer devices will result in better outcomes. But second and more importantly, the time windows allowed for these studies had a negative impact on the results. The IMS III study allowed angiography to begin as long as 5 hours after onset of symptoms and was completed by 7 hours. In the SYNTHESIS trial, the intravenous tPA group was treated on average 1 hour faster than the endovascular intervention group. In MR RESCUE, mean time to enrollment was 5.5 hours and extended up to 8 hours.

We know from experimental studies in animals as well as humans that speed and time to revascularization has a profound impact on outcome. We constantly state that "time is brain" and urge our physicians to institute thrombolysis as fast as possible. Yet, these studies all had delays in the institution of treatment, often due to the extensive diagnostic studies that were part of the protocols. In this situation "perfect is the enemy of good." The future studies must have protocols that limit the diagnostic studies to only what is absolutely necessary to make a triage decision — intravenous thrombolysis or intra-arterial clot extraction. Then we will need to repeat these studies using the newest devices in the shortest time window possible. Imaging studies will have to follow treatment and not delay it. Time is still the enemy, and remains the single most important variable that influences the results of therapies. Although it is certainly important and intellectually interesting to evaluate the penumbra and the collaterals, we cannot allow those studies to slow us down in our attempts to treat patients. New trials must reflect real-world practice issues, or we will not make the progress we are seeking. I would propose a simple clinical scale and rapid CT or MRI as we are currently performing it, and then an immediate decision to go to the angiography suite for interventional clot retrieval or standard therapy. Any further delays will result in worse outcomes. I am optimistic that future studies, if properly designed, will show that new interventional techniques will improve the clinical outcomes for patients with acute ischemic stroke. ■

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3. Kidwell CS, et al, for the MR RESCUE Investigators. A trial of imaging selection and endovascular treatment for ischemic stroke. *N Engl J Med* 2013; [Epub ahead of print] DOI: 10.1056/NEJMoa1212793.
4. Chimowitz M. Endovascular treatment for acute ischemic stroke — Still unproven. *N Engl J Med* 2013; [Epub ahead of print].

immunoblot assay. Among the 44 HSE patients tested, 13 (30%) were found to have IgG, IgM, or IgA antibodies against N-methyl-D-aspartate receptor (NMDAR). HSE cases were associated with anti-NMDAR but not with a large panel of other onconeuronal antibodies (i.e., anti-Hu, -Yo, -Ri, -Ma, -CV2, -amphiphysin) nor with antibodies against other specific synaptic proteins (AMPA receptor, GABAb-receptor or VGKC-complex). These anti-NMDAR antibodies were specific to samples from HSE patients; none were present in the serum or CSF of 20 control patients with either PCR-confirmed enterovirus or VZV encephalitis.

The authors emphasize that the presence of anti-NMDAR antibodies is not equivalent to the diagnosis of anti-NMDA receptor encephalitis, a distinct disorder affecting primarily young women with or without tumor association (usually teratoma of the ovary). Anti-NMDAR encephalitis is characterized by acute psychiatric manifestations, seizures, dyskinesias, hypoventilation, and autonomic instability, and is generally responsive to immunotherapy. The median age of most patients with anti-NMDAR encephalitis is ~20 years and most have normal or only mild abnormalities on MRI brain, moderate CSF pleocytosis, and normal or mildly increased CSF protein

concentration. In contrast, the patients with HSE and NMDAR antibodies in this study were generally older and had higher levels of CSF pleocytosis and protein concentration, suggesting a more intense inflammatory response. Patients with anti-NMDAR encephalitis almost always have CSF antibodies, whereas some of the HSE patients in this study had NMDAR antibody only in serum. A subset of HSE patients in this study had evidence of intrathecal production of IgG antibodies directed against NR1a subunit of the NMDA receptor (similar to classical anti-NMDAR encephalitis); however, the majority of the anti-NMDAR antibodies found in HSE were either a different antibody class (IgA or IgM) or were specific for a different epitope of NMDAR.

Although the pathogenic role for NMDAR antibodies is well established for antibodies of the IgG classes, IgM antibodies had not been previously observed and their significance is unclear. The authors demonstrated that IgM antibody positive sera from patients, but not negative control sera, can downregulate NMDAR and synaptic proteins when co-cultured with mouse primary hippocampal cell cultures. These results are similar to the functional effect on hippocampal cultures previously shown for anti-NMDAR IgG from NMDAR encephalitis patients. This suggests that the anti-NMDAR antibodies in patients with HSE could be pathogenic.

■ COMMENTARY

A coincidence of HSE and anti-NMDAR encephalitis in these patients is theoretically possible but appears unlikely given the low incidence of both diseases and the clinical differences between anti-NMDAR encephalitis and HSE mentioned above. It seems more likely that viral infection causes destruction of neurons initiating a primary autoimmune response against NMDAR in some patients. This might occur by a mechanism involving release and presentation of tissue that is normally shielded by the immune privilege of the central nervous system.

A key question is whether the anti-NMDA antibodies detected in HSE are clinically significant or simply bystander markers of tissue destruction and immune activation. The clinical characteristics of antibody-negative vs antibody-positive patients were examined in this study and no statistically significant difference was found between the two groups regarding response to treatment with acyclovir, the presence of seizures, or neuropsychological or psychiatric symptoms. The only difference found was a significantly longer time between prodromal signs and clinical admission ($P < 0.05$) in the antibody-positive cohort. Unfortunately, this retrospective study was limited by small sample size and lack of long-term follow-up, so no conclusions could be made beyond the acute phase of encephalitis. To elucidate whether the subgroup of patients with HSE and NMDAR antibodies may benefit from immunotherapy, prospective studies with longer follow-up during the time after viral clearance has been achieved are needed. These studies should include screening of all antibody classes. ■

Subcutaneous IVIG for Chronic Inflammatory Demyelinating Polyneuropathy

ABSTRACT & COMMENTARY

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: *Compared to intravenous immunoglobulin, subcutaneous administration of immunoglobulin appears to have equal efficacy with more patient convenience.*

Source: Markvardsen LH, et al. Subcutaneous immunoglobulin in responders to intravenous therapy with chronic inflammatory demyelinating polyradiculoneuropathy. *Eur J Neurol* 2013; Jan. 7, 2013. DOI: 10.1111/ene.12080; [Epub ahead of print].

Is the subcutaneous administration of immunoglobulin (SCIG) as safe and effective as intravenous immunoglobulin (IVIG) for the treatment of chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) as it is for multifocal motor neuropathy and primary immune disorders? To answer this question, 30 IVIG-responding, CIDP patients were recruited for a randomized, double-blind, placebo-controlled trial to receive subcutaneous injections, 2-3 times weekly for 12 weeks, of either their prestudy IVIG dose or saline. Injection volume was never more than 20 mL per injection site, and patients received anywhere from 30-300 mL per week, over 30-120 minutes per infusion period. All patients had previously received IVIG every 3-10 weeks. Exclusionary criteria included age younger than 18 years or older than 80 years, malignancy, pregnancy, coagulopathy, or drug allergy. No patient had previously received SCIG. Muscle strength, measured by the same neurologist and performed by isokinetic dynamometry using four pre-selected muscle groups individualized to each patient's weakness, was the primary endpoint, with secondary endpoints encompassing muscle strength

of nine bilateral muscle groups using a modified Medical Research Council (MRC) scale and a grip strength test averaged over three attempts for each hand. Patients were evaluated 2 weeks pre-study initiation, at study initiation, and at 10 and 12 weeks. At the first and last evaluation, additional measurements obtained included an Overall Disability Sum Score (ODSS), grading arm and leg disability on a scale of 0 (normal) to 12 (total disability), a nine-hole-peg test (9-HPT), and a 40-m-walking test (40-MWT). Statistical analysis included the paired and unpaired t-test, with significance achieved at $P < 0.5$.

Of 40 patients screened, 30 fulfilled entry criteria and 29 were allocated to treatment, 14 to SCIG and 15 to saline, with one patient withdrawing prior to informed consent. Both groups were comparable with respect to duration of CIDP, weekly immunoglobulin dose, degree of disability, MRC score, grip and isokinetic strength, and functionality as measured by 9-HPT and 40-MWT. Compared to the saline group, which deteriorated over the course of the 12-week study, SCIG treatment resulted in significant improvement of all parameters except for 9-HPT, including ODSS, isokinetic strength, MRC and grip strength, and 40-MWT. Redness at the injection site was reported in six SCIG and two saline-treated patients, with rash and itching in two and one SCIG patients, respectively. No patient reported any generalized symptoms. At study end, when asked which was preferred, 20 of 29 enrollees stated a preference for SCIG over IVIG due to improved flexibility with daily life, enhanced strength stability, milder side effects, and shorter infusion times. SCIG appears to be a safe, efficacious, and attractive alternative to IVIG for the treatment of CIDP.

■ COMMENTARY

SCIG may be as effective as IVIG, with improved patient convenience and lower cost, but its mechanism of absorption is incompletely understood. Uptake through blood and lymphatic capillaries, transport through the extracellular matrix, and pre-systemic elimination influence its absorption, which is also impacted by the anatomic site of injection. Rat studies investigating the slow subcutaneous infusion of rituximab suggest that in addition to the site and dose of injection, neonatal Fc receptor-mediated transport is also a major determinant of subcutaneous absorption of monoclonal antibodies.[1] ■

Reference

1. Kagan L, Mager DE. Mechanisms of subcutaneous absorption of rituximab in rats. *Drug Metab Dispos* 2013;41:248-255.

Abnormal Thalamocortical Structural and Functional Connectivity in Juvenile Myoclonic Epilepsy

ABSTRACT AND COMMENTARY

By Nitin K. Sethi, MD

Assistant Professor of Neurology, Weill Cornell Medical College

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

Synopsis: *In patients with juvenile myoclonic epilepsy, abnormal structural and functional connectivity was noted in the anterior thalamocortical bundle, as compared to healthy controls, and was correlated with the severity of the seizures.*

Source: O'Muircheartaigh J, et al. Abnormal thalamocortical structural and functional connectivity in juvenile myoclonic epilepsy. *Brain* 2012;135:3635-3644.

JUVENILE MYOCLONIC EPILEPSY (JME), SOMETIMES CALLED Janz syndrome, is the most common idiopathic generalized epilepsy and is characterized by multiplicity of seizure types, including myoclonic jerks on awakening, generalized tonic-clonic seizures, and absence seizures. The interictal electroencephalogram is characterized by 4-6 Hz generalized spike wave and polyspike wave discharges with amplitude predominance bifrontally. Diffusion tensor imaging and functional magnetic resonance imaging show abnormal anterior thalamocortical bundle structural and functional connectivity in JME patients as compared to healthy controls.

The authors investigated thalamocortical structural and task (phonemic verbal fluency) modulated functional connectivity using diffusion tensor imaging and functional magnetic resonance imaging in 28 patients with JME and compared them to 38 healthy controls. Abnormal structural and functional connectivity was noted in the anterior thalamocortical bundle as compared to healthy controls. The authors further found that the degree of abnormal connectivity was related to disease severity. Patients with active generalized tonic-clonic seizures had greater degree of structural and functional connectivity dysfunction between the basal ganglia-thalamus-supplementary motor area/prefrontal cortex. The authors hypothesize that this dysfunction is the likely explanation of the frontal cortex dysexecutive, verbal and attentional neuropsychological impairments commonly seen in patients with JME.

■ **COMMENTARY**

Previous studies have shown increases in blood oxygen level-dependent (BOLD) activity in the cortex and decreases in thalamic BOLD activity in patients with idiopathic generalized epilepsies and also a faster rate of thalamic volume loss in pediatric patients with idiopathic generalized epilepsies.[1] The above study further strengthens the evidence for structural and functional dysfunction in the basal ganglia-thalamus-cortical (anterior frontal and premotor) loop in patients with JME and helps to explain the frontal lobe dysfunction and impairment in verbal and attention tasks in these patients. ■

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.

CME Instructions

To earn credit for this activity, follow these instructions:

1. Read and study the activity, using the provided references for further research.
2. Log on to www.cmecity.com to take a post-test; tests can be taken after each issue or collectively at the end of the semester. First-time users will have to register on the site using the 8-digit subscriber number printed on their mailing label, invoice or renewal notice.
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5. Once the completed evaluation is received, a credit letter will be e-mailed to you instantly. You will no longer have to wait to receive your credit letter!

Reference

1. Hamandi K, et al. BOLD and perfusion changes during epileptic generalized spike wave activity. *Neuroimage* 2008;39:608-618.

CME Questions

1. What imaging modalities have been proven to be useful in selecting acute stroke patients for endovascular treatment?
a. CT
b. MRI
c. CT and MRI
d. None of the above

2. Which of the following regarding treatment of ischemic stroke is *not* true?
a. Time to reperfusion is the most important variable that determines outcome.
b. Older patients have worse outcomes than younger patients.
c. Large vessel occlusions have a worse outcome than small vessel occlusions.
d. Intra-arterial interventions result in better outcomes than intravenous therapies.

3. Most cases of Alzheimer's disease have a known genetic cause.
a. True
b. False

4. Which of the following statements is *not* true regarding HSE encephalitis?
a. There can be significant morbidity and mortality in HSE even after treatment with antiviral therapy.
b. HSE and anti-NMDAR encephalitis can both show temporal lobe involvement on MRI and pleocytosis in the CSF.
c. HSE primarily affects young women.
d. Anti-NMDA antibodies may be present in some patients with HSE.

5. Subcutaneous administration of immunoglobulin is:
a. less time consuming than the intravenous infusion of immunoglobulin.
b. allows for more flexibility with daily life.
c. appears to cause no systemic side effects.
d. results in little rash or itching.
e. All the above

6. Which of the following statements regarding juvenile myoclonic epilepsy is true?
a. Juvenile myoclonic epilepsy is a type of partial (focal) epilepsy.
b. Patients with juvenile myoclonic epilepsy have myoclonic jerks and generalized tonic-clonic seizures but no absence seizures.
c. Juvenile myoclonic epilepsy is not associated with dysfunction in the thalamocortical structural and functional connectivity.
d. Juvenile myoclonic epilepsy is associated with dysfunction in the thalamocortical structural and functional connectivity leading to impairments in executive functioning and in verbal and attention tasks.

In Future Issues:

Update on Movement Disorders

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When One Antihypertensive Med is Not Enough: Which Combination?

Source: Kato J, et al. *J Am Soc Hypertens* 2012;6:393-398.

THE ALLHAT TRIAL IS THE LARGEST HYPERtension clinical trial ever done, originally enrolling more than 42,000 individuals. That trial concluded that a thiazide diuretic (chlorthalidone) was at least as good as — and in some situations superior to — a calcium channel blocker ([CCB] amlodipine) or an angiotensin converting enzyme inhibitor ([ACE] lisinopril), and that an alpha blocker (doxazosin) was inferior to any of the three others.

But ALLHAT also demonstrated that only about 25% of hypertensives are able to maintain control on one medication. So, when one antihypertensive med is not enough, which combination should we choose?

The ACCOMPLISH trial was the first to address this question on a large-scale basis (n = 11,506) by directly comparing ACE/CCB (benazepril/amlodipine) with ACE/diuretic (benazepril/hydrochlorothiazide). In this trial, outcomes were superior for ACE/CCB.

Not everyone can tolerate an ACE, most commonly due to cough. Kato et al performed a clinical trial to compare in 58 hypertensive elderly patients (mean age, 72 years) the efficacy of an angiotensin receptor blocker (ARB)/CCB (mostly olmesartan/amlodipine) with ARB/diuretic (mostly olmesartan/indapamide).

At the conclusion of the trial, the ARB/CCB combination provided superior blood pressure reduction to ARB/diuretic. The diuretic used in ALLHAT was chlorthalidone, which is definitely more potent than hydrochlorothiazide; whether substitution of chlorthalidone for indapamide in this trial might have tipped the scales in another direction remains unknown. ■

Vitamin D for Osteoarthritis: NOT

Source: McAlindon T, et al. *JAMA* 2013; 309:155-162.

FOR A BURGEONING POPULATION OF BABYboomers who wish to continue being physically active despite advanced years, tools to provide symptomatic relief from osteoarthritis (OA) are valuable (e.g., topical and systemic NSAIDs, opioids, physical therapy), but disease-modification is really the "holy grail." At the current time, we do not possess any disease-modifying pharmacotherapy for OA.

Since vitamin D (VID) is an important player in bone health, might it influence symptoms or disease progression of OA? McAlindon et al performed a 2-year randomized, placebo-controlled trial of VID in subjects with symptomatic OA of the knee. VID dose was titrated from 2000 IU/d up to as much as 8000 IU/d, depending on attainment of a goal plasma VID level between 36-100 ng/mL. In this population of mostly Caucasian adults (mean age, 62 years) living in the Boston area, it is perhaps not surprising that baseline levels of VID averaged 22 ng/mL.

At the end of the trial, no effect (positive or negative) was seen from supplementation with VID on either OA symptoms or evidence of disease progression as measured by degree of cartilage loss. ■

Early Identification of COPD Exacerbations

Source: Yanez AM, et al. *Chest* 2012; 142:1524-1529.

ACUTE EXACERBATIONS OF CHRONIC OBstructive pulmonary disease (AECOPD) are consequential: 10% of patients admitted to the hospital die, 25% of those admitted to the ICU die, and the mortality rate in the year following an AE-COPD hospitalization for those who are discharged home is as high as 43%. Even after successful recovery from an AE-COPD, decrements in pulmonary function from pre-event status are noted that are not regained. Early identification of AE-COPD, with an intent-to-treat with minimum delay, might possibly alter the ominous natural history of AE-COPD.

Historically, it has been shown that the increasing dyspnea characteristic of AECOPD typically begins about 5 days before patients seek consultation from their clinician. For asthma, wider swings in variation between morning and evening peak flow rate herald an acute deterioration, even before patients are overtly symptomatic. In a similar vein of thought, the authors postulated that changes in respiratory rate would signal an impending AE-COPD.

Oxygen-dependent COPD patients (n = 89) were asked to monitor respiratory rate daily for 3 months. Monitoring of daily respiratory rate (DRR) was performed automatically by installing a monitoring device to the patients' oxygen delivery systems. Although respiratory rate was monitored at three different times each day, only the mean DRR rate was used for evaluation.

During 3 months of follow-up, 30 of

the 89 patients required hospitalization for AE-COPD. Baseline average DRR for the group as a whole was 16 breaths/minute; among the subgroup ultimately admitted for AE-COPD, baseline DRR was 15.2. In the 5 days prior to an AE-COPD admission, their DRR increased to 19.1, but no meaningful change in DRR was seen in patients not requiring hospital admission. DRR may provide a new window into early identification of AE-COPD. ■

CKD: Consistency of GFR and Albuminuria as Risk Predictors

Source: Hallan SI, et al. *JAMA* 2012;308: 2349-2360.

Clinicians have become increasingly aware of the disease burden associated with chronic kidney disease (CKD), especially since the routine inclusion of a calculated estimated glomerular filtration rate (eGFR) within metabolic profile testing. Promulgation of CKD stages by national organizations and encouragement of clinicians to consider referral of patients with CKD at an earlier stage (usually by CKD stage 3-B) has prompted the clinical community to address eGFR as well as the presence, absence, and severity of urinary albumin excretion on a more consistent basis. Because of inherent renal functional decline associated with increased age, accompanied by decrease in muscle mass that contributes to the generation of creatinine, some have questioned whether current stratification of CKD by eGFR, albuminuria, or both holds true throughout the lifespan.

Hallan et al performed a meta-analysis on data from more than 2 million individuals in Asia, Australasia, Europe, and North/South America to investigate whether eGFR and the presence of albuminuria remain consistently predictive of adverse outcomes.

Although at older ages the *absolute* risk imparted by CKD was greater than in younger folks (simply because a larger absolute number of older individuals die than younger individuals, whether or not they have CKD), overall, the hazard ratio (HR) for mortality decreased with increasing age. For example, at an eGFR of 45 mL/min, the HR for death (when compared to a normal eGFR) was 3.5 for persons ages 18-54, 2.2 for ages 55-64, and 1.35 for ages > 75 years. A similar relationship was noted for albuminuria.

Albuminuria and reduction in eGFR are associated with adverse outcomes throughout the lifespan, although the HR for risk appears to lessen as we age. ■

Changing Outcomes for Patients with Chronic Hepatitis C

Source: van der Meer AJ, et al. *JAMA* 2012;308:2584-2593.

Chronic hepatitis C (HEPC) has an increased risk for liver cancer, end-stage liver disease, and all-cause mortality. Fortunately, current antiviral treatments for HEPc (e.g., ribavirin and interferon) are effective in the majority of subjects. As many as 80% of HEPc patients who complete a therapeutic course will obtain what is called a sustained virological response (SVR); that is, no detectible HEPc virus 6 months *after* completion of therapy. SVR might reasonably be titled "cure," since indications are that absence of virus at 6 months is indicative of permanent eradication.

Nonetheless, some patients enjoying SVR already have experienced inflammatory hepatic changes resulting in fibrosis. It has not been sufficiently elucidated whether achievement of SVR ultimately reduces risk for mortality, liver cancer, or hepatic failure, especially in a group with already established hepatic fibrosis.

Using an international multicenter database (n = 540), the outcomes of HEPc patients with long-term follow-up (mean 8.4 years), as well as biopsy-proven fibrosis, were investigated to compare those who attained SVR vs those who did not. The mortality rate was essentially three times greater in those who did not attain SVR (26% vs 8.9%); the comparative cumulative incidence rate of liver-related mortality or transplantation was even more dramatic: 1.9% (SVR) vs 27.4% (SVR not attained). The attainment of SVR is associated with substantial long-term reductions in mortality as well as less need for liver transplantation. ■

Is Fructose a Primary Culprit in Obesity?

Source: Page KA, et al. *JAMA* 2013;309: 63-70.

Sorting out the causes of the current pandemic of obesity has not been easy and appears to have contributions from various life quadrants: activity, genetics, absolute calorie ingestion, and — most recently — characteristics of the calories we ingest. For instance, whereas in the recent past one might simplistically think that a gram of ice cream and a gram of broccoli should result in similar metabolic impact, recognition of the glycemic index (variation in glucose rate of absorption from different food sources) has taught us that a calorie is not necessarily always a calorie in the grander scope of things.

Fructose, an increasingly commonplace component of fast foods, snacks, etc., has recently come under fire as a potential culprit exacerbating the obesity pandemic. Mechanistically, fructose could be metabolically detrimental because (compared to glucose, that is) it blunts satiety-inducing GLP-1, and fails to shut off appetite-stimulating ghrelin.

Page et al measured regional cerebral blood flow in response to glucose and fructose ingestion. They found that fructose did not produce the same reduction in hypothalamic cerebral blood flow (associated with satiety and fullness) as did glucose. Disproportionate consumption of fructose may be a significant contributor to weight management problems. ■

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Aspirin Use and Age-Related Macular Degeneration

In this issue: Aspirin use and AMD risk; using NSAIDs and antihypertensive agents; and FDA actions.

Does aspirin cause AMD?

Does regular aspirin use put patients at risk for age-related macular degeneration (AMD)? That is the finding in a highly publicized study from Australia published in *JAMA Internal Medicine* (formerly *Archives of Internal Medicine*). A prospective analysis was conducted from an Australian population-based cohort that included four examinations in 15 years as well as questionnaires regarding aspirin use. Of the 2389 participants with follow-up available, 257 (10.8%) were regular aspirin users and 63 of these (24.5%) developed neovascular (wet) AMD. Regular aspirin users were more likely to develop neovascular AMD: The 15-year cumulative incidence was 9.3% in aspirin users and 3.7% in non-users. After adjustment for age and multiple cardiovascular risk factors, regular users of aspirin had an odds ratio of neovascular AMD of 2.46 (95% confidence interval [CI], 1.25-4.83). The association showed a dose response effect, with daily users at higher risk. Aspirin was not associated with geographic atrophy (dry AMD). The authors conclude that "regular aspirin use is associated with increased risk of incident neovascular AMD independent of a history of cardiovascular disease and smoking." (*JAMA Intern Med* published online Jan. 21, 2013. doi:10.1001/jamainternmed.2013.1583). A related editorial points out that age-related AMD is the leading cause of blindness in Western countries, and this study suggests that regular aspirin is associated with an approximate 2.5-fold greater risk in incident AMD. The study is not a randomized trial, and although there is some biological plausibility in the association between aspirin use and development of AMD, this study is "not sufficiently robust to be clinically directive." (*JAMA Intern Med* published online Jan. 21, 2013. doi:10.1001/jamainternmed.2013.2530.) The take-home message for now is that for patients who are likely to benefit from aspirin (secondary prevention of cardiovascular disease), practice should not change. However, for those patients who take aspirin for indications that are less compelling, we may want to rethink the recommendation until good trials on the relationship between aspirin use and AMD can be assessed. ■

NSAIDs and antihypertensive agents

Mixing certain antihypertensive agents with nonsteroidal anti-inflammatory drugs (NSAIDs) increases the risk of renal failure, according to a new study. In a retrospective cohort study of nearly 500,000 users of antihypertensive drugs in the United Kingdom, rate ratios of acute kidney injury associated with current use of certain antihypertensive agents with NSAIDs were assessed. After a mean follow-up of 5.9 years, 2215 cases of acute kidney injury were identified. Overall, current use of a single antihypertensive (either diuretics, angiotensin-converting enzyme inhibi-

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tors [ACEIs], or angiotensin receptor blockers [ARBs]), along with an NSAID was not associated with increased rate of acute injury. However, combining a diuretic with either an ACEI or ARB along with an NSAID increased the rate of acute kidney injury significantly (rate ratio 1.31, 95% CI, 1.12-1.53). This 31% increased risk of acute kidney injury was driven by a nearly two-fold increased risk in the first 30 days of use. The authors conclude that triple therapy consisting of diuretics with an ACEI or ARB along with an NSAID was associated with an increased risk of acute kidney injury, especially at the start of treatment (*BMJ* published online January 8, 2013. doi.org/10.1136/bmj.e8713). ■

FDA actions

An advisory committee to the FDA has recommended moving hydrocodone/acetaminophen (Vicodin, Norco) from schedule III to schedule II later this year. The move would put the drug in the same category as morphine and oxycontin, and would require a handwritten, tamper-proof prescription for every prescription and refill. Vicodin — the most widely prescribed drug in this country — is at the center of the controversy regarding prescription drug abuse, which has become "epidemic" in this country, according to the CDC. The United States consumes 99% of all the hydrocodone produced worldwide, and deaths attributable to prescription opioid abuse skyrocketed in the last 2 years, outpacing deaths from illegal opioid drugs, including heroin. The move is supported by some advocacy groups, including an endorsement by the American Academy of Pain Medicine, but not by others. Some physicians are concerned that the schedule change will be a major inconvenience for legitimate pain patients and their physicians, who will be required to write a tamper-proof prescription for each refill of the drug.

The FDA has approved an over-the-counter version of topical oxybutynin for the treatment of overactive bladder in women ages 18 and older. The approval is for women only, with oxybutynin available to men by prescription only. The anticholinergic drug has been used for years by prescription for this indication. In studies of more than 5000 subjects, it was determined that consumers can understand the labeling and "properly select whether the product is right for them." Merck will market the product as a patch that is replaced every 4 days under the trade name Oxytrol for Women.

The FDA has lowered the recommended doses for zolpidem (Ambien) for women. The agency based its recommendation on findings that the popular insomnia drug might impair alertness the next morning if taken at recommended doses. The recommendation is also based on findings that zolpidem stays in the body longer than previously thought, especially in women who process the drug somewhat slower. The new recommended maximal dose for women has been lowered from 10 mg to 5 mg for the immediate-release product, and from 12.5 mg to 6.25 mg for the extended-release (Ambien CR). The FDA further recommends that zolpidem and all insomnia drugs should be used at the lowest dose needed to treat symptoms in both men and woman.

The FDA has approved alogliptin for the treatment of type 2 diabetes. The drug is the fourth dipeptidyl peptidase-4 inhibitor after sitagliptin (Januvia), saxagliptin (Onglyza), and linagliptin (Tradjenta). Takeda Pharmaceuticals has been seeking approval for more than 5 years, dealing with the FDA's tighter standards for new diabetes drugs. The approval was based on 14 trials involving about 8500 patients as well as five ongoing postmarketing trials. The agency also approved two additional combinations of alogliptin with metformin and pioglitazone. Alogliptin alone will be marketed as Nesina, alogliptin/metformin will be marketed as Kazano, and alogliptin/pioglitazone will be marketed as Oseni. Both combination products carry boxed warnings (for lactic acidosis associated with metformin and heart failure associated with pioglitazone). All three are distributed by Takeda Pharmaceuticals.

Johnson & Johnson is one step closer to approval of canagliflozin, the first of a new type of diabetes drug. The Endocrionologic and Metabolic Drugs Advisory Committee voted 10 to 5 in favor of approving the drug while still expressing some concern about the cardiovascular safety of the agent. Canagliflozin is an oral inhibitor of the sodium glucose cotransporter 2 (SGLT2) that reduces reabsorption of glucose in the kidney, resulting in increased urinary glucose excretion with a consequent lowering of plasma glucose levels as well as weight loss. If eventually approved by the FDA, it would be the first SGLT2 inhibitor on the U.S. market. The FDA denied a similar drug 1 year ago (dapagliflozin) because of increased risk of bladder and breast cancer. The favorable vote was based on clinical trials of more than 10,000 patients worldwide which showed that the drug improves blood sugar levels and led to modest weight loss as well as reduction in blood pressure. ■