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INSIDE

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Switching to a New Epilepsy Drug: Is New Always Better?

ABSTRACT & COMMENTARY

By Padmaja Kandula, MD

Assistant Professor of Neurology and Neuroscience, Comprehensive Epilepsy Center, Weill Cornell Medical College

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

Synopsis: *This randomized, single-center trial compared the efficacy and tolerability of monotherapy substitution with levetiractam vs carbamazepine and valproic acid in patients who failed initial treatment with first-generation antiepileptic agents.*

Source: Hakami T, et al. Substitution monotherapy with levetiracetam vs older antiepileptic drugs. *Arch Neurol* 2012;68:1563-1571.

Based on the prior work of Patrick Kwan and Martin Brodie,[1] the effectiveness of the first antiepileptic drug (AED) in new-onset epilepsy is nearly 50%. Conversion to a different monotherapy is then necessary for those who fail to become seizure-free or do not tolerate the initial agent. However, despite this common clinical scenario, very few evidence-based recommendations exist in the literature to guide clinicians. This clinical conundrum becomes further complicated by the existence of more than a dozen antiepileptic medications to choose from. In this randomized, single-center, open-label trial, the authors compare substitution monotherapy with levetiracetam, vs carbamazepine or valproic acid in those patients who have failed their first AED therapy.

Patients who failed initial monotherapy with either carbamazepine, phenytoin, or valproic acid for partial epilepsy based on efficacy or tolerability were eligible for this study. Patients were excluded on the basis of severe intellectual impairment; history of major psychiatric morbidity;

Look for Expanded Stroke Alert in March

The monthly column, Stroke Alert, does not appear in this issue. Expanded stroke coverage will be published in the March 2013 issue.

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history of substance abuse; recent (within 3 months) use of anxiolytic, antidepressant, or mood-altering substances; and pregnancy or intended pregnancy.

Eligible patients were then randomized for substitution monotherapy with either levetiracetam or a first-generation older antiepileptic agent, either extended-release carbamazepine or valproic acid. If the initial AED was carbamazepine or phenytoin, the patient was randomized to either levetiracetam or valproic acid. If the initial AED was valproic acid, the patient was then subsequently randomized to carbamazepine or levetiracetam. During a 4-week titration phase, the initial AED was weaned and the substituted AED was increased in twice weekly increments to a target dose of 1000 mg for both levetiracetam and valproic acid and 400 mg for carbamazepine. Subsequent adjustment was then left to the discretion of the treating neurologist. In pragmatic fashion, if seizures were uncontrolled on the allocated study drug, adjunctive therapy with another agent could be initiated. In addition, if adverse effects were intolerable with the randomized agent, patients were allowed to withdraw from the study altogether.

The primary outcome measures were improvement in quality of life (QOL) and depression as compared to baseline at 3 months post-randomization, based on the Hospital Anxiety and Depression Scale (HADS) and the 89-item QOL inventory report. Secondary outcomes included depression and QOL (89-item inventory) at 12 months, changes in anxiety symptomatology, Liverpool Adverse Events Profile (LAEP) scores, formal cognitive function testing, seizure counts (excluding those during cross taper phase), medication compliance, and treatment failure. All the above assessments were performed at baseline, 3, 6, and 12 months post-randomization.

At study onset, 51 patients were randomized to levetiracetam and 48 to the older generation AED treatment group (25 and 23 to valproic acid and carbamazepine, respectively). Six patients were excluded due to study noncompliance, one to medication adverse effects (levetiracetam), one to conversion to high-grade brain tumor (levetiracetam), and two deaths (one patient secondary to sudden unexplained death in epilepsy on carbamazepine and an unrelated stomach carcinoma on levetiracetam).

With regards to primary outcome, there was no difference in the HADS depression score from baseline to 3 months in the levetiracetam group (39.5% improvement) vs the older generation AED group of carbamazepine and valproic acid (34.1% improvement). Interestingly, there was a significant proportion of patients with improvement in the 89-item QOL epilepsy inventory score in the older generation AED group (71%) vs the levetiracetam group (48.8%) at 3 months.

In terms of secondary outcomes, there was no clinically significant difference in HADS depression scores at 12 months between the levetiracetam (42.9%) vs the older AED group (46.3%). The HADS anxiety scores improved in both treatment groups at 3 months (48.8% levetiracetam group vs 54.6% old AED) and 12 months (52.4% vs 61% with levetiracetam and older AED group, respectively) with, again, no clinically significant difference. At 12 months, there was no clinically significant difference (62.8% levetiracetam vs 65.8% old AED group) between the groups in 89-point QOL inventory. No significant difference in global vs specific drug adverse side effects or neurocognitive assessments were noted between the two groups at all time points. Finally, there were no significant differences in seizure counts between the two groups at all designated follow-up intervals.

■ COMMENTARY

The above results show that substitution monotherapy with levetiracetam vs traditional first-generation AEDs, such as carbamazepine or valproic acid, did not show any clinically significant difference in improvement in depression, QOL, anxiety, efficacy, retention rate, adverse side effects, or neurocognitive performance. Over time, both groups showed similar and sustained improvement in QOL measures, anxiety symptomatology, and side effect profile. Although the authors failed to prove their original hypothesis that levetiracetam monotherapy substitution over older AED treatment has better neurocognitive and QOL measures, this trial does have a few important reassuring clinical implications. First, switching a patient from an ineffective or intolerable drug can result in better neurocog-

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Editorial E-Mail: leslie.coplin@ahcmedia.com
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Questions & Comments
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nitive and psychosocial measures. Second, the widespread clinical belief that levetiracetam has a greater tendency to exacerbate mood disorders was not borne out in this study. Both the HADS depression and anxiety scores and mood adverse side effects (LEAP scores) were no different between both groups even at the 12-month mark. On the negative side, the lack of a clinically significant difference between new (levetiracetam) and old (carbamazepine, valproate) AED substitution monotherapy highlights the ongoing need for further controlled studies to systematically compare new AEDS with older agents in refractory partial epilepsy to formulate rational therapy. ■

Reference

1. Kwan P, Brodie MJ. Early identification of refractory epilepsy. *N Engl J Med* 2000;342:314-319.

Myasthenic Antibodies and Disease Phenotype

ABSTRACT & COMMENTARY

By Michael Rubin, MD

Professor of Clinical Neurology, Weill Cornell Medical Center

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

Synopsis: *There are clinical differences in patients with myasthenia gravis, based on which antibody type is present in the serum — acetylcholine receptor antibodies, muscle-specific kinase antibodies, clustered-receptor antibodies, or seronegative patients.*

Source: Oh SJ, et al. Different characteristic phenotypes according to antibody in myasthenia gravis. *J Clin Neuromusc Dis* 2012;14:57-65.

DO THE PRESENCE OR ABSENCE OF ACETYLCHOLINE RECEPTOR (AchR)-binding antibodies (Abs) and muscle-specific kinase (MuSK) Abs correlate with disease phenotype in myasthenia gravis (MG)? To address this question, retrospective review was undertaken of the clinical, laboratory, and electrodiagnostic data of 235 MG patients seen between May 1, 2003, and January 1, 2008, at the University of Alabama Neuromuscular Disease Clinic, in Birmingham, Alabama. Patients were divided into those positive for AchR Abs, those positive for MuSK Abs, and those seronegative for both AchR and MuSK Abs. Diagnosis of MG was based on the presence of fluctuating muscle weakness, in conjunction with either positive AChR binding Abs, positive MuSK Abs, abnormal decrement on repetitive nerve stimulation testing performed on four muscles (abductor digiti minimi, flexor carpi ulnaris, orbicularis oris, and trapezius), abnormal jitter on single-fiber electromyography of the extensor digitorum communis (EDC) muscle, or frontalis muscle if the former was normal. Ocular MG was diagnosed when this was the solitary finding and persisted for 2 or more years, bulbar MG when respiratory or pharyngeal muscle involvement was evident, and severity of disease was determined using the MG Foundation of America classification. Statistical analyses included the unpaired t test and Pearson X2 test, with P values < 0.05 considered statistically significant.

AChR Ab-positive MG peaked at 20-29 years of age, mostly in women, and again at 60-69 years of age, mostly in men, whereas MuSK Ab-positive MG plateaued over 3 decades, from 10-39 years of age, with a mean age of onset of 32.6 years. Seronegative MG plateaued over 4 decades, from 30-69 years of age. AChR Abs were positive in 68.5% (161 cases) and MuSK Abs in 6.4% (15 cases), the latter more commonly in African Americans (7 of 49, 14%) than whites (8 of 186, 4%). African Americans were also over-represented in the AChR Ab-negative generalized MG group, 50% vs 17%, whereas they were under-represented in AChR Ab-positive ocular MG, (25%, vs 68.4% white patients). Hence, African Americans are more commonly MuSK positive, as are women compared to men, whereas whites are more commonly ocular with AChR Ab positivity. Purely ocular MG, which comprised 11.5% of all MG, was always MuSK-negative, and comprised 20.3% of those seronegative. Of those presenting with ocular MG, 54% remained so at 2 years, and those positive for AchR Abs were more likely to generalize. Seronegative MG tended to have a milder form at presentation, and rarely experienced respiratory difficulty or myasthenic crisis. Those with MuSK Abs tended to be predominantly faciobulbar, and never harbored a thymoma, which was found predominantly in AchR Ab-positive MG. Response to edrophonium, anticholinesterase, and intravenous immunoglobulin was poor in MuSK-positive MG, but long-term outcome was similar in all three groups.

■ COMMENTARY

Among patients with generalized MG, 80-85% demonstrate antibodies directed against the acetylcholine receptor (AchR-Abs), 5-8% have antibodies against muscle-specific kinase, and 10% are said to be seronegative. *Clustered* AChR-Abs, initially termed low-affinity AchR-Abs, are present in approximately 60% of patients with seronegative *generalized* myasthenia, and are detected by immunofluorescence assay, based on binding of IgG1 to AChRs expressed in a cell line and clustered by rapsyn, the intracellular scaffolding protein.[1] Among patients with seronegative *ocular* myasthenia, up to 50% appear to have clustered AChR-Abs which, when injected intraperitone-

ally into mice, can passively transfer disease and hence appear to be pathogenic, with mechanisms similar to those seen with typical AChRs.[2] It appears that even seronegative myasthenia is, in the majority of cases, autoimmune in nature. ■

References

1. Leite MI, et al. IgG1 antibodies to acetylcholine receptors in "seronegative" myasthenia gravis. *Brain* 2008;131(Pt 7):1940-1952.
2. Jacob S, et al. Presence and pathogenic relevance of antibodies to clustered acetylcholine receptor in ocular and generalized myasthenia gravis. *Arch Neurol* 2012;69:994-1001.

A Trial of Intracranial Pressure Monitoring in Traumatic Brain Injury — What Do We Do Now?

ABSTRACT & COMMENTARY

By Halinder S. Mangat, MD

Assistant Professor of Clinical Neurology, Weill Cornell Medical College

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

Synopsis: *Intracranial pressure (< 20 mmHg)-guided therapy in patients with severe traumatic brain injury was not shown to be superior to care based on imaging and clinical examination.*

Source: Chesnut RM, et al. A trial of intracranial-pressure monitoring in traumatic brain injury. *N Engl J Med* 2012;367:2471-2481.

Chesnut et al have performed the first randomized, controlled trial to evaluate the benefit of intracranial pressure (ICP) monitoring on outcome after severe traumatic brain injury (TBI). The study compares ICP-guided therapy to therapy based on clinical examination and periodic CT-based brain imaging. It was conducted at five centers in Bolivia and one in Ecuador. Patients were included if they arrived within 24 hours of injury, had a closed head injury, had a Glasgow Coma Scale (GCS) score of ≤ 8, a motor score of ≤ 5 if intubated, and were randomized within 24 hours of injury or within 24 hours of deterioration to a GCS of ≤ 8. Patients were excluded if they had a GCS of 3 with bilateral fixed and dilated pupils. There was a decision to not actively treat before enrollment, if there was no ICU bed or no ICP monitor available, if the patient had a non-survivable injury, if the patient was pregnant or a prisoner, or if there was no informed consent. The treatment protocol included basic nursing monitoring and care measures, prophylaxis, and thresholds for laboratory measures. Routine CT scans were obtained on admission, 48 hours, and 5-7 days after the first scan in the imaging group. Intracranial hypertension was treated by tiered algorithms, which were similar in both groups and were titrated to ICP < 20 mmHg or utilized based on imaging and clinical examination.

Six-month outcome, which was a composite of 21 components including survival and neuropsychological testing, was not different in the two groups. Thirty-day mortality was 21% in the ICP monitoring group and 30% in the imaging-medical examination group. However, this difference was not statistically significant. Six-month mortality was 39% in the ICP monitoring group and 41% in the imaging-clinical exam group.

■ COMMENTARY

The Brain Trauma Foundation has developed guidelines for the management of severe TBI. ICP (and cerebral perfusion pressure)-guided therapy is a central tenet of the TBI guidelines. As there have not been any randomized, controlled trials demonstrating a direct benefit of ICP monitoring in improving outcomes, it is a level II and III recommendation.[1] The recommendation is based on studies showing improved outcome in patients treated utilizing ICP monitoring compared to historical controls, small non-randomized studies, and studies published from prospectively collected observational data. Furthermore, the threshold of 20 mmHg at which ICP must be treated is also a level II recommendation.[2] In spite of these recommendations in the TBI guidelines, there has been doubt over the direct benefit from ICP monitoring, and whether elevated ICP is merely a marker of severity of injury.

In a retrospective study, Badri et al demonstrated the prognostic correlation of average ICP in the first 48 hours with mortality, and functional and neuropsychological outcome at 6 months.[3] They found that the unadjusted odds ratio for death was 2.33 per 10 mmHg increase in average initial 48-hour ICP. However, within survivors there was no association between average ICP and neuropsychological function.

In separate publications from prospectively collected data from the New York state TBI-trac database, Ghajar and colleagues demonstrated significantly lower mortality in patients who underwent ICP monitoring (19.6%; n = 1084) vs patients who did not undergo ICP monitoring (33.2%, n = 223) following severe TBI.[4] These are robust data as the two groups were controlled for covariates that affect outcome: age, GCS, pupillary reactivity, brain CT findings, and hypotension. They further demonstrated that patients with ICP monitoring who responded to ICP-lowering therapy had a significantly lower risk of death at 2

weeks (14.7%, n = 95) than those who did not respond (31.4%, n = 274), after adjustment for independent factors as above.[5]

The trial by Chesnut et al is very well conceived, executed, and remarkable for the high follow-up rate of 92%. However, there are some shortcomings. Thirty-nine percent of patients screened were excluded from the study. Only 45% of patients were transported by ambulance, likely implying inadequate pre-hospital care. This potentially placed the patients at risk of hypoxia and hypotension, which are both highly important pre-hospital factors that influence outcome. In some cases, arrival at hospitals was several hours after injury, further prolonging this vulnerability and duration of insults. The patients were also a severely injured group, with a median GCS of 4, one or both pupillary abnormalities in 44%, midline shift > 5 mm in 36%, and compressed mesencephalic cisterns in 85% of patients. This may make the findings less applicable to less severely injured patients. The Kaplan-Meier survival plot appeared to show early differences in survival between the two groups at day 14, but this trend was slowly reversed over the period of the study. Mortality almost doubled in the ICP group between the initial 30-day period and 6 months. This is most likely related to post-hospital health care systems or lack thereof. The highest mortality in TBI patients tends to be in the first 2 weeks. Therefore, the initial 30-day mortality difference of 21% vs 30% in the ICP and imaging group, respectively, is important. There appears to be a tendency of benefit in the ICP monitoring group, even if it is not statistically significant. And this lack of significant difference may be influenced by prehospital factors such as hypotension and hypoxia, which could have blunted the outcome differences.

In summary, while this is a historic trial, the takeaway message must not be to stop pursuing ICP monitoring in patients with severe TBI. As highlighted above, the results of the trial leave some important unanswered questions. One must contemplate carefully the use of different treatments instituted for ICP-directed therapy. Perhaps the adverse effects of these therapies also offset some benefit that is gained by ICP monitoring. It has been shown that adoption of Brain Trauma Foundation guidelines has decreased overall mortality from TBI. Therefore, this apparent contradiction must be handled with care until further convincing data are available, and ICP monitoring should be continued. Clinical examination and imaging should be performed as often as possible. And we must be circumspect of the targets we set for ICP treatment and the therapies we choose. ■

Reference

1. Brain Trauma Foundation; American Association of Neurological Surgeons; Congress of Neurological Surgeons; Joint Section on Neurotrauma and Critical Care, AANS/CNS. Bratton SL, et al. Guidelines for the management of severe traumatic brain injury. VI. Indications for intracranial pressure monitoring. *J Neurotrauma* 2007;24(Suppl 1):S37-S44.
2. Brain Trauma Foundation; American Association of Neurological Surgeons; Congress of Neurological Surgeons; Joint Section on Neurotrauma and Critical Care, AANS/CNS. Bratton SL, et al. Guidelines for the management of severe traumatic brain injury. VIII. Intracranial pressure thresholds. *J Neurotrauma* 2007;24(Suppl 1):S55-S58.
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4. Farahvar A, et al. Increased mortality in patients with severe traumatic brain injury treated without intracranial pressure monitoring. *J Neurosurg* 2012;117:729-734.
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MRI to Visualize Progression in Parkinson's Disease

ABSTRACT & COMMENTARY

By Claire Henchcliffe, MD

Associate Professor of Neurology and Neuroscience, Weill Cornell Medical College

Dr. Henchcliffe reports she is on the speakers bureau and advisory board for Allergan and Teva; speakers bureau for Boehringer-Ingelheim, GlaxoSmith-Kline, and Novartis; advisory board for Merz; and is a consultant for Gerson Lehman Group and Guidepoint Global.

Synopsis: *This case-control study uses multi-spectral structural MRI sequences to examine two areas of tissue volume loss at different stages of Parkinson's disease (PD). Data support involvement of the substantia nigra at earlier stages of PD than basal forebrain.*

Source: Ziegler DA, et al. Substantia nigra volume loss before basal forebrain degeneration in early Parkinson disease. *Arch Neurol* 2012; Nov 26:1-7 [Epub ahead of print].

The investigators aimed to determine whether substantia nigra pars compacta (SNc) degeneration occurs earlier in Parkinson's disease (PD) than basal forebrain (BF) degeneration, as predicted by the influential "Braak hypothesis" that proposes a characteristic pattern of temporal progression of PD pathology. Participants included 29 subjects with PD, with mean age 65.3 (± 8.8) years, mean Mini Mental Status scores of 28/30 (± 1.6), with more right- than left-sided symptom onset. Subjects were divided into groups comprising PD Hoehn and Yahr (H&Y) stage 1 (unilateral symptoms), and H&Y stages 2 + 3 (bilateral symptoms, with or without postural instabil-

ity, independently ambulating). Those in H&Y stage 1 had shorter disease duration (3.1 ± 1.4 years) and lower impairment judged by the Unified Parkinson's Disease Rating Scale (UPDRS) (9.2 ± 5.4 points) compared with H&Y stages 2 + 3 (4.8 ± 2.9 years' duration, 19.7 +/- 8.3 UPDRS points), although only the difference in UPDRS points met statistical significance. A group of 27 healthy control subjects were matched for age, gender, and years of education. All participants underwent MRI scans using a 3 Tesla magnet, and high-resolution multispectral data included multi-echo magnetization-prepared rapid gradient echo with T1 weighting, 3-dimensional (3D) T2-weighted turbo-spin echo, multi-echo fast low angle shot with proton density weighting, and 3D T2-weighted FLAIR turbo-spin echo sequences. In PD H&Y stage 1, the left SNc was smaller than in controls ($P = 0.001$; right side not significant). For those with PD H&Y stages 2 + 3, both left and right SNc volumes were significantly smaller than controls but not PD H&Y stage 1. In contrast, BF volumes in subjects with PD H&Y stage 1 were not significantly different from controls, but those with PD H&Y stages 2 + 3 had significantly reduced BF volume vs controls (left: $P = 0.008$; right: $P = 0.01$), and PD H&Y stage 1 ($P = 0.04$ on the left side; right side not significant).

■ COMMENTARY

Current understanding of the spread of PD pathology postulates that alpha-synuclein pathology, reflected by Lewy bodies and Lewy neurites, begins in the peripheral autonomic nervous system, and then involves the central nervous system, specifically, the olfactory bulb and medulla early on, progressing rostrally to involve the basal forebrain cortex. This neuropathologic pattern reflects the clinical motor findings and non-motor features such as constipation and olfactory dysfunction, which may appear years before motor symptoms. This pattern also explains the cognitive decline related to cortical involvement later in the disease. However, it has been difficult to directly confirm this pattern of spread due to limited biomarkers of regional neuronal loss. The authors chose two critical structures: the dopaminergic SNc, responsible for the vast majority of motor dysfunction in PD, and the cholinergic BF, associated with developing cognitive decline in PD. According to the Braak hypothesis, SNc is affected prior to BF involvement. The finding that SNc volume is measurably decreased in PD at both early and later stages, and that BF volume loss is only significant in later stages, certainly is consistent with the Braak hypothesis, and makes clinical sense. However, just as Braak's study examining patterns of alpha-synuclein pathology only tells a part of the story, so it is with MRI. The Braak hypothesis does not address neurotransmitter changes that might occur prior to alpha-synuclein pathology. MRI likewise is unable to measure these changes. Previous studies support loss of cholinergic forebrain neurons in early PD, and it would be helpful to correlate volumetric MRI and nuclear imaging of specific neurotransmitters. Moreover, a longitudinal study will be extremely important. Despite this, the investigators demonstrate that the days of using MRI simply to rule out other processes may soon be over. Other studies have demonstrated cortical thinning, especially frontotemporal, global gray matter and amygdala atrophy, and decrease in olfactory bulb volume (although this last is not in all studies) in PD. The sophisticated multispectral MRI techniques that the investigators have developed now make possible the types of studies being undertaken in other neurodegenerative disorders such as Alzheimer's and Huntington's disease. Finally, not only does this approach advance understanding PD progression as a whole, it will be invaluable in monitoring differences between individuals. ■

EEG and MRI Findings in Children with Febrile Status Epilepticus

ABSTRACT & COMMENTARY

By Sotirios Keros, MD, PhD

Instructor, Department of Pediatrics, Division of Pediatric Neurology, Weill Cornell Medical College

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

Synopsis: *Focal EEG slowing is the most common abnormality seen after febrile status epilepticus, and is associated with radiologic hippocampal injury.*

Source: Nordli DR Jr, et al. Acute EEG findings in children with febrile status epilepticus: Results of the FEBSTAT study. *Neurology* 2012;79:2180-2186.

Although many children with a first febrile seizure will have had a simple febrile seizure, a relatively common and benign childhood illness, a subset will present in febrile status epilepticus, the most severe in the spectrum of febrile seizures. Despite the risks, most children with febrile status epilepticus will have very good outcomes. On the other hand, febrile status epilepticus is associated with medically refractory temporal lobe epilepsy with variable prognosis. However, prospective study data are lacking.

In this paper, the authors investigated EEG and MRI abnormalities associated with febrile status epilepticus from the ongoing, prospective Consequences of Prolonged

Febrile Seizures (FEBSTAT) study. Children eligible for enrollment were between 1 month and 5 years of age and presented with febrile seizures (temperature > 101° F) lasting > 30 minutes and did not otherwise have a history of febrile seizures, acute brain injury or infection, or severe neurologic disability. EEGs were obtained within 72 hours, and were interpreted by multiple investigators in a blinded manner. MRIs were also interpreted by radiologists blinded to the clinical history.

Of the 199 children enrolled, 58% were younger than 18 months of age, 53% were male, 57% had continuous febrile status epilepticus, 86% were developmentally normal, and 80% had no history of prior febrile seizure. The peak median temperature was 102.7° F (IQR 101.5°-103.5° F) and the median duration of seizures was 70 minutes (IQR 47-110). Focal status epilepticus was present in 68%.

Fifty-five percent of all EEGs were considered to be normal. Only 7% of the EEGs had epileptiform activity, primarily in the form focal sharp waves or spikes, of which half were located in a temporal lobe. Non-epileptiform abnormalities were noted in 43% of the children, consisting of focal slowing (24%), diffuse slowing (11%), and focal attenuation (13%). Of the 47 cases with significant focal slowing, 45 were in the temporal region. Focal slowing was more common on the right (77%) as was focal attenuation (60%). There were 19 children who had both lateralizing seizures and focal slowing or focal attenuation. Of these, in 79%, the EEG abnormality was on the expected side, while in 21% it was contralateral to the side of the expected cortical origin of the seizure based on lateralizing signs.

MRI abnormalities were noted in approximately 23% of study patients. MRI abnormalities, primarily of the hippocampus, were positively associated with focal slowing or attenuation on EEG, with hippocampal T2 signal changes showing the strongest association. In a previous paper based on the same group of patients,[1] there were no hippocampal T2 signal abnormalities in a control group of 96 children who presented with only simple febrile seizures as opposed to those with febrile status epilepticus.

■ COMMENTARY

This is a much-needed study that hopefully will provide, in the future, an opportunity to answer the question of whether febrile status epilepticus is indeed a risk factor for hippocampal sclerosis and medically refractory temporal lobe epilepsy. Very few patients had any epileptiform activity on EEG, but almost half had slowing or attenuation, a marker of cerebral dysfunction. As the authors note, this is consistent with a model where status epilepticus leads to brain injury that can in turn cause epilepsy. Ideally, the

study will be able to identify risk criteria based on these early EEG and MRI findings, as well as follow-up EEGs and imaging, and provide an opportunity to test interventions that may prevent intractable epilepsy and improve overall outcomes in those patients most at risk. ■

Reference

1. Shinnar S, et al. MRI abnormalities following febrile status epilepticus in children: The FEBSTAT study. *Neurology* 2012;79:871-877.

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.
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CME Questions

1. Which of the following was *not* a primary or secondary outcome of the epilepsy monotherapy substitution trial?

a. Cognitive function testing
b. Seizure counts
c. Medication adherence
d. Mortality rate
e. Improvement in depression and quality of life measures at 12 months
f. Improvement in depression and quality of life measures at 3 months

2. Which of the following statements is correct?

a. Patients with ocular myasthenia and positive for AchR Abs are more likely to generalize.
b. Response to edrophonium, anticholinesterase, and intravenous immunoglobulin is poor in MuSK positive myasthenia gravis.
c. Clustered AChR-Abs are present in approximately 60% of patients with seronegative generalized myasthenia gravis.
d. Among patients with seronegative ocular myasthenia, up to 50% appear to have clustered AChR-Abs.
e. All of the above are true

3. Intracranial pressure monitoring in patients with severe traumatic brain injury is of proven benefit in reducing mortality.

a. True
b. False

4. Which of the following correctly describes findings of multispectral structural MRI in Parkinson's disease (PD)?

a. Reduction in basal forebrain volume is seen early and throughout the course of PD.
b. Substantia nigra and basal forebrain volume losses correlate with each other.
c. Substantia nigra volume loss occurs in early stages of PD and loss worsens in later stages.
d. Substantia nigra volume loss is seen in early and later stages of PD, while basal forebrain volume loss is observed only in later stages.

5. Which of the following MRI abnormalities was the most strongly associated with focal slowing and focal attenuation in children with febrile status epilepticus?

a. Hippocampal malrotation
b. Cortical dysplasia
c. Hippocampal T2 signal abnormalities
d. Right-sided white matter changes

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By Louis Kuritzky, MD

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Does Screening for Type 2 Diabetes Pay Off?

Source: Simmons RK, et al. Screening for type 2 diabetes and population mortality over 10 years (ADDITION-Cambridge): A cluster-randomised controlled trial. *Lancet* 2012;380:1741-1748.

It is easy to envision that earlier diagnosis of type 2 diabetes (DM2) might lead to an opportunity for earlier, intensified interventions that might translate into improved outcomes. So far, however, we only *think* that, we don't actually *know* it. Simmons et al followed patients from general practices in England (n = 11,737) who enrolled in pathways of 1) screening for DM2 plus intensive multifactorial interventions, 2) screening for DM2 plus routine care, and 3) a "no screening" population. The mean age of the population was 58 years.

The practices in which multifactorial intervention groups were enrolled received educational and logistical support for attaining glucose, blood pressure, and lipid goals. Recent data in the United States suggest that currently fewer than 15% of type 2 diabetics are achieving simultaneous goal attainment in all three of these.

Over an interval of approximately 10 years' follow-up, there were no significant differences seen between unscreened vs screened subjects in regards to all-cause mortality, cardiovascular mortality, cancer mortality, or diabetes-related death.

Explanations for failure to reduce risk include the following: 1) screening for diabetes became more routine in the non-screened group over time; 2) routine care is improving, such that intensive intervention may not be as dramatically different than routine care, and 3) the duration of follow-up was insufficient. ■

Surgical Treatment of Diabetes

Source: Vetter ML, et al. Comparison of bariatric surgical procedures for diabetes remission: Efficacy and mechanisms. *Diabetes Spectrum* 2012;25:200-210.

The link between obesity and type 2 diabetes (DM2) is widely acknowledged. Certainly, weight gain is associated with increased incidence of DM2, and weight loss improves insulin sensitivity, as well as other cardiovascular risk factors. Surgery produces prompt and dramatic reductions in excess body weight, yet it appears that rebalancing of the disturbed metabolic homeostasis seen in DM2 varies among the different bariatric surgical interventions. Additionally, it appears that weight loss alone cannot fully explain the metabolic restorations seen post-surgically. Favorable metabolic changes are especially prompt, intensive, and durable when surgery involves bypassing or elimination of much of the small intestine from the digestive path.

In their review of the DM2 bariatric surgery trials, Vetter et al conclude that the primary driving force for DM2 remission appears to be weight loss. Since diversionary procedures are associated with greater and more durable weight loss, they would be anticipated to produce greater benefits for DM2 and they do. Overall adjustable gastric bypass is reported to result in remission in 57% vs 95% in biliopancreatic diversion surgery. The long-term relapse rate is not insubstantial: One very long follow-up of diversionary surgery (up to 16 years) noted relapse in 43%.

There are distinct hormonal changes that differ between the surgical interventions. For instance, gastric banding does not affect incretin activity, but bypass surgeries are associated with increased secretion of incretins. Evidence continues to accumulate that corroborates the efficacy, safety, and durability of bariatric surgical intervention for DM2. ■

Benefits and Consequences of Aldosterone Antagonists for HF

Source: Hernandez AF, et al. Associations between aldosterone antagonist therapy and risks of mortality and readmission among patients with heart failure and reduced ejection fraction. *JAMA* 2012;308:2097-2107.

Clinical trial data have conclusively demonstrated improved mortality and cardiovascular outcomes in chronic heart failure (CHF) patients who receive aldosterone blockade (ALD) with spironolactone or eplerenone in addition to standard of care treatment. Clinical trial populations, however, are different from practice settings in which patients may not enjoy the same risk:benefit balance as the often highly selected subjects who enroll in clinical trials.

To evaluate outcomes among patients

with newly administered ALD *not* enrolled in a clinical trial, Hernandez et al reviewed 2005-2010 Medicare data on older (mean age, 78 years) patients who had received a new ALD prescription on discharge from the hospital for CHF (n = 5887). They looked at all-cause mortality, cardiovascular readmission, heart failure readmission, and hyperkalemia.

Although there was no difference in total mortality, the addition of ALD to the treatment regimen was associated with lower heart failure readmission. On the other hand, patients treated with ALD were statistically significantly more likely to be readmitted with hyperkalemia over the next year (1.5-2.5 times more likely). ALD treatment offers some positive outcomes, but clinicians must be vigilant for hyperkalemia when ALD treatment is chosen. ■

Long-term Prevention of Recurrent DVT

Source: Brighton TA, et al. Low-dose aspirin for preventing recurrent venous thromboembolism. *N Engl J Med* 2012; 367:1979-1987.

Current guidelines for management of venous thrombosis (e.g., the Antithrombotic 9 guideline published by the American College of Chest Physicians in 2012) suggest that after an initial episode of unprovoked deep venous thrombosis (DVT), it is reasonable to provide at least a 3-month course of anticoagulation, with consideration of a longer interval on a case-by-case basis. Usually, anticoagulation is not continued long-term. But the risk of DVT recurrence after cessation of coumadin is not insignificant.

Aspirin (ASA) is easy to administer and has a generally favorable risk profile. After cessation of coumadin, Brighton et al compared DVT patients treated with aspirin vs placebo for approximately 3 years. Although numerically fewer recurrent DVT episodes occurred in the ASA group, the numbers did not achieve statistical significance (4.8%/yr vs 6.5%/yr; P = 0.09). On the other hand, ASA produced a reduction in secondary composite outcomes, which included myocardial infarction, stroke, and cardiovascular death. Hence, even though ASA did not produce a statistically significant reduction in DVT, the potential reduction in other cardiovascular adversities might tip the balance toward benefit. Because the primary endpoint of the trial was not met, secondary endpoints, however, must be considered hypothesis generating rather than conclusive. ■

Marijuana and the Risk of Schizophrenia

Source: Evins AE. The effect of marijuana use on the risk for schizophrenia. *J Clin Psychiatry* 2012;73:1463-1468.

The recent legalization of marijuana in two states has brought the discussion of potential toxicity to the fore. Although it is unclear what impact legalization will have on epidemiology of marijuana use, most experts agree that more widespread and heavier marijuana use would not be at all surprising. The psychiatry community has particular concern about marijuana use because observational data suggest that early (during adolescence) marijuana use is associated with an increased risk for an earlier onset of schizophrenia.

Most schizophrenia is genetic in origin (80%). Hence, if marijuana is a contributor to schizophrenia, it occurs in a minority of cases. On the other hand, some genetic predilection for development of schizophrenia can be seen in carriers of the Met allele of the COMT gene, who appear especially likely to develop psychosis subsequent to cannabis use in adolescence.

At the current time, experts suggest advising parents that marijuana use in adolescence, especially heavy use, may increase the risk of future schizophrenia, and for persons with existing psychosis, may make symptoms worse. ■

Losartan Improves Erectile Function in Diabetics

Source: Chen Y, et al. Losartan improves erectile dysfunction in diabetic patients: A clinical trial. *Internat J Impot Res* 2012; 24:217-220.

Animal studies have shown that high levels of angiotensin II (ANG2) in the corpora cavernosa of the penis extinguish erections, the effect of which can be blocked by losartan, an ANG2 receptor blocker. Whether losartan might have a favorable effect on erectile dysfunction (ED) in diabetic humans has not been definitively confirmed.

Chen et al studied diabetic adults with ED (n = 124) who were randomized to receive either LOS 50 mg/d alone, tadalafil 5 mg/d (TAD) alone, the combination of LOS + TAD, or no treatment for 12 weeks. Persons with poorly controlled hypertension were excluded from the trial.

At the conclusion of the trial, TAD and LOS provided comparable significant improvements in erectile function scores, but the LOS + TAD combination was significantly better than either monotherapy. The control group experienced no significant improvement in erectile function. LOS was very well tolerated, and tolerability was not compromised by combining LOS + TAD. Clinicians might consider the addition of LOS to patients with insufficient ED response to TAD alone. ■

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PHARMACOLOGY WATCH

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FDA Approves Apixaban for Patients with Nonvalvular AF

In this issue: Apixaban approval; new dental clinical practice guideline; apixaban for VTE; aspirin resistance; tamoxifen treatment; and FDA actions.

Apixaban superior to warfarin in trial

The FDA has approved apixaban — the long-awaited third novel oral anticoagulant (NOAC) — for the prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation (AF). The drug follows dabigatran (Pradaxa) and rivaroxaban (Xarelto) for this indication, which has been traditionally treated with warfarin. The safety and efficacy of apixaban was demonstrated in the 18,000 patient ARISTOTLE trial, which showed that in patients with nonvalvular AF, apixaban was superior to warfarin in preventing stroke and systemic embolism, caused less bleeding, and resulted in lower mortality than warfarin. The FDA will likely allow the manufacturers of apixaban to market the drug as "superior to warfarin." Apixaban is dosed twice a day, similar to dabigatran; rivaroxaban is dosed once a day. Apixaban and rivaroxaban are factor Xa inhibitors, while dabigatran is a direct thrombin inhibitor. No head-to-head studies have been done among the three NOACs, which are expected to compete aggressively for this lucrative market that is worth billions of dollars in sales. All three lack a reversal agent, which could potentially increase the risk of serious bleeding. Apixaban is marketed as Eliquis by Bristol-Myers Squibb and Pfizer. ■

New dental prophylaxis guideline

The American Academy of Orthopedic Surgeons (AAOS) and the American Dental Association (ADA) have jointly published a clinical practice guideline regarding dental prophylaxis in patients with orthopedic implants. The recommendations, which are based on very limited evidence, state that, "the practitioner might consider discontinuing the practice of routinely prescribing prophylactic antibiotics for patients with hip and knee prosthetic joint implants undergoing dental procedures." The guideline further states that they are unable to recommend for or against topical oral antibiotics in patients with implants, but they do recommend that patients with joint implants should "maintain appropriate oral hygiene," even though there is no evidence regarding this recommendation. This guideline does little to settle the debate between orthopedic surgeons, who often recommend lifetime dental prophylaxis, and infectious disease specialists who generally recommend against dental prophylaxis after 1 year. This rather weakly worded guideline is probably not the guidance most primary care physicians were hoping for, since they are generally responsible for prescribing prophylactic antibiotics and are responsible for possible adverse effects. The full guideline is available at www.aaos.org/research/guidelines/PUDP/dental_guideline.asp. ■

Length of treatment for VTE

How long should we treat patients with venous thromboembolism (VTE)? VTE includes deep-vein thrombosis and pulmonary embolism. Current

This supplement was written by William T. Elliott, MD, FACP, Chair, Formulary Committee, Kaiser Permanente, California Division; Assistant Clinical Professor of Medicine, University of California-San Francisco. In order to reveal any potential bias in this publication, we disclose that Dr. Elliott reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study. Questions and comments, call: (404) 262-5404. E-mail: neill.kimball@ahcmedia.com.

guidelines recommend 3-6 months of anticoagulation for unprovoked VTE — usually low-molecular weight heparin followed by warfarin. A new study suggests that an additional year of the factor Xa inhibitor apixaban (recently approved for stroke prevention in nonvalvular atrial fibrillation, see page 1) may be beneficial for these patients. In an industry-sponsored study, patients with VTE who had completed 6-12 months of anticoagulation therapy were randomized to an additional 12 months of apixaban (2.5 or 5 mg twice a day) or placebo. Nearly 2500 patients were included in the intention-to-treat analysis. Recurrent VTE or death from VTE occurred in 73 of 829 patients randomized to placebo (8.8%) compared to 14 of 840 patients on 2.5 mg of apixaban (1.7%) and 14 of 813 patients on 5 mg of apixaban (1.7%; $P < 0.001$ for both comparisons). The rates of major bleeding were 0.5% in the placebo group and 0.2% and 0.1% in the apixaban 2.5 mg and 5 mg groups, respectively. The rate of death from any cause was 1.7% in the placebo group and 0.8% and 0.5% in the apixaban 2.5 mg and 5 mg groups, respectively. The authors conclude that extended anticoagulation with apixaban at either a treatment dose (5 mg bid) or thromboprophylactic doses (2.5 mg bid) reduced the risk of recurrent VTE without increasing the rate of major bleeding (*N Engl J Med* published online Dec. 8, 2012. doi: 10.1056/NEJMoa1207541). In this study, the majority of patients were younger than age 75 without other comorbities such as low body weight or renal impairment. It is also unknown if the results of this study are applicable to other approved anticoagulants such as rivaroxaban. ■

Aspirin resistance and enteric coating

Could "aspirin resistance" be due to enteric coating? The concept of aspirin resistance is very controversial with some experts suggesting that it does not exist. A new study suggests that enteric coating of aspirin may be partially responsible for "pseudoresistance." Researchers recruited 400 healthy volunteers who were then screened for their response to a single, oral dose of 325 mg immediate-release or enteric-coated aspirin. Variable absorption caused nearly half of those taking enteric-coated aspirin to have apparent resistance (49%), while this was not seen in any of the subjects taking immediate-release aspirin. On re-exposure, all of those with variable absorption responded to aspirin. The authors conclude that the study failed to identify a single case of true aspirin resistance, but pseudoresistance, reflecting delayed and reduced drug absorption, complicates enteric-coated but not immediate-release aspirin (*Circulation* published online Dec. 4, 2012. doi: 10.1161/CIRCULATIONAHA.112.117283). This study seems to contradict the concept that up to 40% of the population is "aspirin resistant." There is a suggestion that the concept of aspirin resistance has been touted by the manufacturers of expensive brand-name aspirin substitutes. This study may question the wisdom of the routine use of enteric-coated aspirin, especially given that enteric coating has very little benefit with regard to gastrointestinal protection. ■

Is 10 years of tamoxifen better?

Ten years of tamoxifen may be better than the standard 5 years for women with estrogen receptor (ER)-positive breast cancer, according to a new study from the United Kingdom. Researchers randomized about 6800 ER-positive women with early breast cancer who had completed 5 years of adjuvant tamoxifen to another 5 years of treatment or stopping therapy. There were 617 recurrences in the 3428 women who took tamoxifen for 10 years vs 711 in 3418 women who stopped at 5 years ($P = 0.002$). There was also a lower death rate (331 vs 397, $P = 0.01$) and reduced overall mortality (639 vs 722, $P = 0.01$) in the 10-year group. There were higher rates of endometrial cancer (relative risk [RR] 1.74, 95% confidence interval [CI], 1.30-2.34) and pulmonary embolism (RR 1.87; CI, 1.13-3.07) in the 10-year group, but no higher rate of stroke and a lower risk of ischemic heart disease (RR 0.76; CI, 0.60-0.95). The authors suggest that 10 years of tamoxifen in ER-positive patients can approximately halve breast cancer mortality during the second decade after diagnosis (*Lancet* published online Dec. 5, 2012. doi.org/10.1016S0140-6736(12) 61963-1). ■

FDA actions

The FDA has approved pasireotide diaspartate injection for the treatment of Cushing's disease in patients who are not candidates for surgery or for whom surgery has not worked. The drug is considered an orphan drug. The safety and efficacy were evaluated in a trial of 162 patients with Cushing's disease who were randomized to one of two doses of the drug. About 20% of participants had normal urine cortisol levels within 6 months. Side effects included increased blood sugar levels and liver injury. The drug is administered subcutaneously twice a day. It is marketed by Novartis as Signifor. In February 2012, the FDA approved mifepristone (Korlym) for the treatment of Cushing's syndrome. ■