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Vol. 36, Issue 7, March 2017
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Neurology
[ALERT®]

Evidence-based summaries of the latest clinical neurology research

ABSTRACT & COMMENTARY

New Tools for the Diagnosis of CJD

By Joseph E. Safdieh, MD

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

SYNOPSIS: Cerebrospinal fluid analysis using second-generation, real-time, quaking-induced conversion has a high sensitivity and specificity for the diagnosis of Creutzfeldt-Jakob disease.

SOURCE: Foutz A, Appleby BS, Hamlin C, et al. Diagnostic and prognostic value of human prion detection in cerebrospinal fluid. *Ann Neurol* 2017;81:79-92.

Prion diseases are uncommon and invariably fatal neurologic disorders caused by propagation of misfolded proteins from the normal alpha-helix form to the pathogenic beta-pleated sheet form. Prion diseases in humans include Creutzfeldt-Jakob disease (CJD), variant CJD, fatal familial insomnia, and Gerstmann–Sträussler–Scheinker syndrome. Patients are suspected to have CJD when they present with a rapidly progressive dementia often associated with myoclonus and ataxia. Supportive diagnostic testing includes characteristic MRI changes (cortical ribbon and thalamic/basal ganglia hyperintensities on DWI) and associated lumbar puncture characteristics (elevation of the 14-3-3 protein). However, none of these tests provide enough sensitivity and specificity to firmly establish the diagnosis, often necessitating a brain biopsy.

Over the past few years, a novel testing method that can amplify tiny amounts of prion protein in the laboratory, called real-time quaking-induced conversion (RT-QuIC), has been proposed as a more sensitive and specific diagnostic test for CJD. RT-QuIC is performed by mixing recombinant prion protein with small amounts of pathogenic prion protein, which induces the formation of amyloid fibrils that can be detected by thioflavin T staining. In this study, the authors evaluated the sensitivity and specificity of RT-QuIC testing of cerebrospinal fluid (CSF) in patients with suspected CJD. The study had both a retrospective and prospective arm. The study was performed by the National Prion Disease Pathology Surveillance Center, which maintains a detailed database of all referred cases.

Financial Disclosure: *Neurology Alert*'s editor in chief, Matthew Fink, MD, reports he is a consultant for Procter & Gamble. Peer reviewer M. Flint Beal, MD; executive editor Leslie Coplin; editor Jonathan Springston; and AHC Media Editorial Group Manager Terrey L. Hatcher report no financial relationships relevant to this field of study.

Neurology
[ALERT]

Neurology Alert,
ISSN 0741-4234, is published monthly by AHC Media, a Relias Learning company
111 Corning Road, Suite 250
Cary, NC 27518
AHCMedia.com
GST Registration Number: R128870672.
Periodicals Postage Paid at Atlanta, GA 30304 and at additional mailing offices.

POSTMASTER: Send address changes to
Neurology Alert,
P.O. Box 550669,
Atlanta, GA 30355.

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In the study, 2,141 CSF samples were tested with RT-QuIC. In the retrospective cohort of CJD cases (126 patients), 92% of the samples had positive RT-QuIC testing, as compared to 81.7% with elevated 14-3-3 protein. In the prospective cohort of CJD cases (65 patients), 95.4% of the samples had positive RT-QuIC testing, as compared to 81.5% with elevated 14-3-3 protein. Overall sensitivity of the RT-QuIC test (92-95%) was higher than assaying CSF 14-3-3 protein (81.2-81.5%). Of note, in both groups, approximately 76% of patients had characteristic MRI changes for CJD. Only 29% of patients in the retrospective cohort manifested characteristic EEG changes (periodic sharp waves).

To assess the specificity of the RT-QuIC assay, other rapidly progressive neurologic disorders were used as controls. Of note, the most common neuropathological diagnosis in the non-CJD cohort was Alzheimer's disease. In the prospective cohort, none of the non-CJD cases demonstrated abnormal RT-QuIC assays (100% specificity), and in the retrospective cohort, there was one non-CJD case with abnormal RT-QuIC (98.5% specificity). The specificity of the 14-3-3 protein assay was much lower (62% in the retrospective cohort and 48% in the prospective cohort). In the prospective cohort the positive predictive value of RT-QuIC was 100% and of 14-3-3 was 86.9%. The negative predictive value was 82.4% for RT-QuIC and 50% for 14-3-3.

■ COMMENTARY

This study contributes valuable additional experience with RT-QuIC testing in the diagnostic workup of suspected CJD. Other studies have assessed RT-QuIC in CSF and even in nasal brushings, demonstrating a high degree of sensitivity and specificity. This study is extremely important because it confirms the diagnostic value of CSF RT-QuIC testing in both a retrospective and a prospective cohort. The test is demonstrated to have higher sensitivity and specificity than 14-3-3 protein and total tau. In the prospective cohort, specificity was 100%, suggesting that this test is highly unlikely to be positive in a non-CJD case. This is a significant advance over 14-3-3, which is sensitive but not very specific. In the setting of an appropriate clinical picture, a positive RT-QuIC test in CSF has a strongly positive predictive value, although it is not 100% sensitive, so a negative test may not exclude the disease. The hope for the near future is that by using a combination of imaging modalities with CSF analysis, we will be able to confidently diagnose CJD without resorting to a brain biopsy. ■

ABSTRACT & COMMENTARY

Ocrelizumab for Multiple Sclerosis

By Jai S. Perumal, MD

Assistant Professor of Neurology, Weill Cornell Medical College

Dr. Perumal reports she receives grant/research support from Genzyme Corp., and is on the speakers bureau for Biogen Idec, Genzyme Corp., Acorda Therapeutics, and Teva Pharmaceuticals.

SYNOPSIS: A Phase III trial of ocrelizumab in primary-progressive multiple sclerosis and two Phase III trials of ocrelizumab in relapsing-remitting multiple sclerosis have demonstrated efficacy with treatment.

SOURCES: Montalban X, Hauser SL, Kappos L, et al.; for the ORATORIO Clinical Investigators. Ocrelizumab versus placebo in primary progressive multiple sclerosis. *N Engl J Med* 2017;376:209-220.

Hauser SL, Bar-Or A, Comi G, et al.; for the OPERA I and OPERA II Clinical Investigators. Ocrelizumab versus interferon beta-1a in relapsing multiple sclerosis. *N Engl J Med* 2017;376:221-234.

Efficacy of Ocrelizumab in Primary-progressive Multiple Sclerosis. No disease-modifying therapy currently is approved for the treatment of primary-progressive multiple sclerosis (PPMS). Several therapies currently approved for relapsing-remitting multiple sclerosis (RRMS) were tested in PPMS, but failed to meet the primary endpoint. Based on emerging data that B cells may play a major role in the pathogenesis of MS and may have a significant role in progressive MS, the authors undertook this study of ocrelizumab for PPMS. Seven hundred thirty-two patients were randomized in a 2:1 distribution to either ocrelizumab or placebo. The dose of ocrelizumab was 600

mg every six months, administered as 300 mg infusions two weeks apart. The primary outcome was 12-week confirmed disability progression. Trial duration was at least 120 weeks of treatment until the occurrences in the trial cohort of 253 instances of disability progression. Disability was defined as a 1-point increase in EDSS for those with EDSS ≤ 5.5 and 0.5-point increase if the baseline EDSS was > 5.5. Key inclusion criteria were patients with PPMS between the ages of 18 and 55 years, EDSS between 3 and 6.5, and presence of either elevated immunoglobulin index or positive oligoclonal bands in CSF.

The primary endpoint was met, with the percentage of patients on ocrelizumab who had disability progression = 32.9% and those on placebo = 39.3% (hazard ratio, 0.76; 95% confidence interval, 0.59-0.98; relative risk reduction, 24%; $P = 0.03$). The secondary endpoints at 24 weeks, confirmed disability and performance on timed 25-foot walk, also were met.

Efficacy of Ocrelizumab in RRMS. Two Phase III clinical trials (OPERA I and OPERA II) were undertaken to evaluate the efficacy and safety of ocrelizumab in RRMS. Ocrelizumab treatment was compared to interferon beta-1a given subcutaneously three times a week. A total of 1,656 patients from these two trials were randomized in a 1:1 manner to receive ocrelizumab 600 mg IV every 24 weeks or interferon beta 1a 44 micrograms three times per week. The duration of the trial was 96 weeks. Key inclusion criteria were MS patients between the ages of 18 and 55 years with EDSS between 0 and 5.5 and at least two clinical relapses within the previous two years or one relapse within the preceding year.

The primary endpoint was annualized relapse rate at 96 weeks. In both OPERA I and OPERA II, it was 0.16 in the ocrelizumab group and 0.29 in the interferon beta group, which indicated a 46% lower rate of relapse ($P < 0.001$). With regard to disability progression, the percentage of patients with disability progression was 9.1% in the ocrelizumab group and 13.6% in the interferon beta group, which represents a 40% lower risk for the ocrelizumab group ($P < 0.001$). Secondary endpoints included MRI outcomes of gadolinium-enhancing lesions and new or enlarging T2 lesions, also in favor of ocrelizumab over interferon beta treatment ($P < 0.003$).

Adverse Events Associated with Ocrelizumab.
ORATORIO Trial. The most frequently reported adverse event was infusion-associated reactions, which were seen in about 40% of patients. Most were not severe and only two patients in the trial withdrew because of infusion reactions. Upper respiratory tract infections were more common in the ocrelizumab group vs. placebo, 10.9% and 5.9%, respectively. Oral herpes also was more common in the ocrelizumab group, 2.3% vs. 0.4%. There was no case of progressive multifocal leukoencephalopathy (PML). During the Phase III trial, 11/486 (2.3%) patients who received ocrelizumab developed malignancies — four patients with breast carcinoma, three patients with basal cell carcinoma, and one each of endometrial carcinoma, anaplastic large cell lymphoma, malignant fibrous histiocytoma, and pancreatic carcinoma. Additionally, one case of basal cell carcinoma and a case of squamous cell carcinoma were reported during the open-label extension phase. In the placebo group, there were two malignancies (0.4%), cervical adenocarcinoma and basal cell carcinoma. There were four deaths in the ocrelizumab group, one each due to pulmonary embolism, pneumonia, pancreatic carcinoma, and aspiration pneumonia.

OPERA I and OPERA II trials. The most common adverse events were infusion-related reactions similar to that reported in the ORATORIO trial. Overall infection rates generally were similar between the ocrelizumab and interferon groups. Herpes infections were more frequent in the ocrelizumab group (5.9% vs. 3.4%). There were no cases of opportunistic infections, including PML. During the trial, there were four malignancies reported (0.5%), and during the open-label extension, there were five more cases. In total, they included four cases of breast carcinoma, two basal cell carcinoma, two malignant melanoma, and one renal cell carcinoma. The interferon group had two reports of malignancy — one mantle cell lymphoma and one squamous cell carcinoma.

■ COMMENTARY

For the first time, a treatment trial for PPMS has had positive results, which is very encouraging for the treatment of primary progressive MS. A prior trial of rituximab, a chimeric anti-CD-20 molecule with a mechanism of action similar to the humanized anti-CD-20 antibody ocrelizumab, did not meet its primary endpoint of efficacy in disability progression. However, a sub-analysis showed that younger patients with gadolinium-enhancing lesions suggestive of active inflammation did show benefit on disability with rituximab treatment. FDA approval of ocrelizumab would be the first approval of a drug for the treatment of PPMS and, hopefully, would make a meaningful difference for patients with PPMS, especially younger patients in delaying disability.

The results of ocrelizumab in RRMS demonstrates high efficacy, making it one of the treatment options for patients with highly active disease. It also offers convenience of administration and less difficulty with compliance, as it will be administered in infrequent infusions every six months.

With regard to adverse events, infusion reactions were common in the ocrelizumab group but were mostly mild or moderate, except for one incidence of bronchospasm. The frequency of infections, including UTIs and respiratory tract infections, did not appear significantly different between the different treatment groups. However, there

were two infection-related deaths, one due to community-acquired pneumonia and one due to aspiration pneumonia, in the ocrelizumab-treated patients in the PPMS trial. No opportunistic infections, including PML, were seen. There were more malignancies reported with ocrelizumab than the other groups, predominantly breast carcinoma. This is a concern that will need further evaluation and close monitoring. An FDA decision regarding approval is expected in March 2017. ■

ABSTRACT & COMMENTARY

Differences in Disease Duration in LBD May Be Related to Pathologic Burden

By Harini Sarva, MD

Assistant Professor of Clinical Neurology, Weill Cornell Medical College; Assistant Attending Neurologist, NewYork Presbyterian Hospital

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

SYNOPSIS: This observational study of 807 autopsy-confirmed cases of Lewy body disease (LBD) used Braak neurofibrillary tangle staging, frequency of neuritic plaques, and Lewy body staging to demonstrate that those individuals who had diffuse LBD had a shorter disease duration than those with transitional LBD localized to the limbic region.

SOURCE: Graff-Radford J, Aakre J, Savica R, et al. Duration and pathologic correlates of Lewy body disease. *JAMA Neurol* 2017; doi:10.1001/jamaneurol.2016.4926 [Epub ahead of print].

This retrospective, observational study of autopsy findings and clinical data from 807 subjects with Lewy body disease (LBD) from the National Alzheimer's Coordinating Center included individuals who had transitional LBD and diffuse LBD. Clinical data included age at onset of cognitive symptoms, sex, Unified Parkinson's Disease Rating Scale scores, Mini Mental State Exams (MMSE), neuropsychological evaluations, age at death, and presence of core dementia with Lewy bodies (DLB) features (hallucinations, fluctuations, parkinsonism, and probable REM sleep behavior disorder [RBD]). The mean age of onset of cognitive decline was 70.9 years, and the mean age at death was 79.2 years. Sixty-three percent were men. Vascular pathology also was assessed — 126/806 had microinfarcts; 94/656 had lacunes; and 36/654 had large vessel infarcts. Of the 255 with transitional LBD, 73.7% met criteria for high or intermediate likelihood of dementia caused by Alzheimer's disease (AD) pathology; 72.6% of 401 subjects with diffuse LBD met criteria for AD. Those with transitional LBD were older at time of death and had less parkinsonism and neuritic plaques compared with those with diffuse LBD.

Of the original 807 subjects, 766 had information on disease duration. Among all 766 subjects, univariate regression models suggested that older age and male sex were associated with shorter disease duration from time of cognitive symptom development. The presence of APOEε4 did not correlate with disease duration. After adjusting for age at onset, gender, and APOEε4 status, higher Braak staging (neurofibrillary tangles in the cortex) and increased frequency of neuritic plaques did not correlate with disease duration. However, between-group comparison suggested that those with diffuse LBD had shorter disease duration compared with those with transitional LBD. After correction for age, gender, APOEε4 status, Braak staging, and frequency of neuritic plaques, the presence of lacunar infarcts was associated with a shorter disease duration.

When specifically analyzing those with clinical diagnosis of DLB during life (n = 238), older age, positive APOEε4 status, and diffuse LBD pathology were associated with shorter disease duration, whereas male gender, Braak staging, neuritic plaques, and transitional LBD were not. When comparing the clinical features of diffuse LBD and transitional LBD, the former had more of the core features of DLB and a faster cognitive decline, not only in the MMSEs but also in the Category Fluency Test and the Wechsler Adult Intelligence Scale—Revised Digit Symbol subtest. Of the four core features of DLB, the two that had the best correlation with shorter disease duration were parkinsonism and probable RBD reported at the final visit.

■ COMMENTARY

DLB is the second most common form of dementia after AD and has a shorter disease duration than AD. Despite known diagnostic criteria, DLB is still difficult to accurately recognize clinically, because of the clinical variability of these patients and the pathological overlap with AD and vascular dementia. Predicting prognosis of these patients is even more challenging. This complexity in diagnosis not only hampers our ability to symptomatically treat early but also to prognosticate and prepare the patient and families for the future course of the disease.

This study by Graff-Radford et al further adds to the un-

derstanding of the different subgroups of LB pathology and the potential clinical trajectories. However, the retrospective, autopsy-driven nature of this study reiterates the need for better diagnostic assessments during life that would enable long-term observational studies of living cohorts. The development of reliable LB pathology-specific functional imaging may aid in better earlier diagnosis, particularly with the presence of AD and vascular pathology in this cohort. With such a high percentage of those with AD-like pathology, the role of amyloid in disease duration was not assessed and also may contribute to shorter disease duration. From a treatment standpoint, we know that atypical parkinsonian patients, such as those with DLB, do not have a consistent robust response to levodopa, yet those with parkinsonism at the final clinical evaluation were found to have a shorter disease duration. Whether parkinsonism correlates to the diffuse pathological changes or motoric issues (falls, contractures from severe rigidity) from poorly treated parkinsonism is unclear. Lastly, the importance of treating vascular risk factors in conjunction with parkinsonism and RBD again is raised, with the correlation between shorter disease duration and lacunar strokes, which not only add to cognitive burden but can lead to significant morbidity. Thus, while adding to our knowledge of pathology, this study highlights the need for the development of reliable biomarkers to study these patients during their lifetimes to accurately correlate clinical findings and prognosis. ■

ABSTRACT & COMMENTARY

Guillain-Barré Syndrome and Hepatitis E

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: Hepatitis E is the most common form of viral hepatitis worldwide and often is asymptomatic. But it is commonly associated with Guillain-Barré syndrome and Guillain-Barré variants.

SOURCE: Stevens O, Claeys KG, Poesen K, et al. Diagnostic challenges and clinical characteristics of hepatitis E virus-associated Guillain-Barré syndrome. *JAMA Neurol* 2017;74:26-33.

Antecedent infection initiating an immune response often is believed to result in Guillain-Barré syndrome (GBS), with prior infection of the gastrointestinal tract, most commonly by *Campylobacter jejuni*, or respiratory tract, noted in two-thirds. Other antecedent infections include human immunodeficiency virus (HIV), influenza, cytomegalovirus (CMV), and Epstein-Barr virus (EBV), and less commonly, varicella-zoster virus, herpes simplex virus, hepatitis A, B, C, and E viruses, *Haemophilus influenzae*, *Escherichia coli*, and *Mycoplasma pneumonia*. Zika virus recently has been identified as causally related to GBS. What is the prevalence and clinical spectrum of hepatitis E (HepE) virus-associated GBS and how may it be accurately diagnosed?

Undertaken at the Department of Neurology, University Hospital, Leuven, Belgium, this retrospective cohort study identified all GBS or GBS-variant patients who presented between Jan. 1, 2007, and Nov. 1, 2015, within four weeks of onset of neurological symptoms. Patients were categorized clinically as pure motor GBS, Miller-Fisher syndrome, Bickerstaff brainstem encephalitis, acute ataxic neuropathy, bifacial weakness with distal paresthesiae, acute multiple cranial neuropathies, pharyngeal-cervical-brachial variant, and overlap syndrome. Clinical history and examination findings, results of lumbar puncture and blood work, including antiganglioside or anti-sulfatide antibodies (IgM and IgG against GM1, GM2, GM3, GM4, GD1a, GD1b, GD2, GD3, GT1a, GT1b, GQ1b, and sulfatides), and infectious serologic serum tests were reviewed. Patients accepted in transfer following intravenous immunoglobulin treatment and those without usable serum in the laboratory serum bank were excluded. Statistical analysis comprised the Shapiro-Wilk normality test and the two-tailed unpaired Mann-Whitney test, with $P < 0.05$ considered significant.

Among 88 patients with GBS or its variant, 73 satisfied inclusionary and exclusionary criteria, encompassing 44 men and 29 women, with mean age 52 years, of which 8% (n = 6) had positive IgM HepE assays, consistent with possible acute HepE infection, two of whom also tested positive for EBV or CMV. Elevated alanine aminotransferase (> 1.5 times the upper limit of normal) was found in four of these patients. Thus, 6% (n = 4) of this GBS cohort had probable acute HepE infection, two presenting with a GBS variant (acute ataxic neuropathy or the pharyngeal-cervical-brachial variant) and the two others with classic GBS. Of the two patients who tested positive for both HepE and CMV or EBV, one had mild predominantly sensory GBS and one had classic GBS. Acute HepE infection is associated with GBS, and elevated alanine aminotransferase may be a clue to its presence.

■ COMMENTARY

Hyper-endemic in many Asian and African developing countries, where infection is caused by HepE virus 1 and 2, and spread via the fecal-oral route through contaminated water, HepE also is endemic in developed countries, where HepE3 and HepE4 are the culprits,

and are porcine zoonoses. Most often asymptomatic, HepE can cause acute and chronic hepatitis, and it is the most common cause of acute viral hepatitis worldwide. HepE is associated with a variety of neurologic disorders, including GBS, which, in 2000, was reported as the first HepE-associated neurologic complication. Other disorders include neuralgic amyotrophy, encephalitis, meningitis, and myelitis. Mononeuritis multiplex often is reported with HepE, as well as a rare report of myositis. Bell's palsy and vestibular neuronitis have occurred concomitantly with HepE, but a causal relationship remains speculative. Hepatitis is either absent or mild when seen in conjunction with neurologic complications of HepE. ■

ABSTRACT & COMMENTARY

EEG Reactivity Testing in Comatose Patients After Severe Brain Injury

By Peter B. Forgacs, MD

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

SYNOPSIS: Studies assessing EEG reactivity in comatose patients after severe brain injuries are highly variable and almost never provide replicable definitions for presence or absence of EEG reactivity, even though it is used increasingly as a prognostic measure.

SOURCE: Admiraal MM, van Rootselaar AF, Horn J. Electroencephalographic reactivity testing in unconscious patients: A systematic review of methods and definitions. *Eur J Neurol* 2017;24:245-254. doi: 10.1111/ene.13219.

Electroencephalography (EEG) traditionally is used to identify potentially reversible causes of altered levels of alertness in hospitalized patients, such as seizures or status epilepticus and metabolic encephalopathy. More recently, however, some EEG features also have been used to assess prognosis of neurological outcomes after severe brain injuries. Notably, the use of EEG to aid prognostication is increasingly explored in comatose post-cardiac arrest patients, especially since various targeted temperature management (TTM) protocols introduced continuous EEG monitoring as standard of care in these patients. In particular, the absence of EEG reactivity is considered to be one of the indicators of poor outcome. Recently, several guidelines, such as the American Heart Association Post-Cardiac Arrest Care Guideline and the European Resuscitation Council and European Society of Intensive Care Medicine Guideline, advised testing of EEG reactivity for consideration as a prognostic marker after cardiac arrest. However, none of these guidelines and not even the American Clinical Neurophysiology Society Standardized Critical Care EEG Terminology provides specific descriptions of stimulus administration and precise definitions for presence or absence of EEG reactivity.

Admiraal et al addressed this shortfall via a systematic review of all studies between 1970 and May 2016 that assessed EEG reactivity. The inclusion criteria were reports of original research studies in English or Dutch that involved adult patients who were unconscious at the time of testing as a result of a severe brain injury from any etiologies. The authors identified 40 articles based on these criteria and assessed their methodological quality using the QUality In Prognostic Studies (QUIPS) tool. In addition, the authors also rated the descriptions of stimulus protocol and reactivity definitions using a four-category grading scale based on the level of reproducibility.

According to the QUIPS assessments, most studies had reasonably good overall quality. However, descriptions of stimulation protocols and definitions of EEG reactivity definitions were highly variable. While 33/40 studies did specify their stimulation protocol, only three described it in sufficient detail to be exactly replicable. All studies used at least auditory stimulation, but most studies also reported highly variable combination of additional stimuli, including noxious, visual, and sensory stimulations. Of the 27/40 articles that reported their definition of EEG reactivity, none reported it in sufficient detail to be exactly replicable. The authors concluded that EEG reactivity testing clearly is not standardized and descriptions of stimulus protocols and precise definitions of EEG reactivity are highly insufficient in the current literature.

■ COMMENTARY

The major finding of this review is that methods of stimulation to elicit EEG reactivity are highly variable and the studies examined almost never provide replicable definitions. As new therapeutic interventions and advancements in acute medical care have led to improved survival and neurological outcomes after severe brain injuries, many previously accurate predictive indicators of outcomes in these patients have become less reliable. As a result, major efforts are now devoted to finding early but accurate prognostic factors applicable to everyday clinical practice, which often is strained to simultane-

ously provide the best possible treatment to those who have potential for good recovery while limiting care that is futile. However, a major concern is that even though prognostication criteria for outcomes are still evolving in some instances, withdrawal of life-sustaining therapy (WLST) decisions continue to drive mortality in patients who do not readily regain consciousness after severe brain injuries. In addition, in some cases, even well-designed, large, multicenter trials, have high rates of WLST, which carry the risk of self-fulfilling prophecies that may affect outcomes. These considerations highlight the need for rigorous examination of studies assessing accuracy of prognostic factors, as done in this current review, and put emphasis on the ethical obligation to include only clearly defined and highly reproducible prognostic markers in future guidelines.

Based on the findings of this review, future studies aimed to assess EEG reactivity in comatose patients should use a clear protocol for stimulus delivery, use multiple types of stimuli (i.e., auditory, noxious, visual), and apply them multiple times to ensure reproducibility. They should also describe the exact timing of stimulation in relation to time of injury; document concurrent use of sedative medications or other treatments that may affect EEG reactivity (such as hypothermia); and define clear thresholds for changes in EEG frequency, amplitude, and waveforms (e.g., stimulus induced discharges). Importantly, large, prospective, multicenter trials should be conducted based on such reproducible criteria before EEG reactivity is included in prognostication guidelines.

This study also strongly highlights the general need for precise definitions in assessments of any prognostic factor that is intended to be used in prognostication of comatose patients with severe brain injuries. This is especially important as many times these factors influence withdrawal of life-sustaining therapy decisions. Future prospective studies aimed to develop or validate prognostication guidelines should include only highly accurate and reproducible clinical or diagnostic assessments. ■

ABSTRACT & COMMENTARY

First-ever Study of Genome Sequencing in the Common Forms of Epilepsy

By M. Elizabeth Ross, MD, PhD

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

SYNOPSIS: In the first study with genome sequencing in the common forms of epilepsy, ultra-rare genetic mutations of known epilepsy genes were over-represented in the epilepsy population, compared to controls.

SOURCE: Epi4K consortium; Epilepsy Phenome/Genome Project. Ultra-rare genetic variation in common epilepsies: A case-control sequencing study. *Lancet Neurol* 2017;16:135-143.

Heritability studies have identified dozens of genes in which mutations can lead to rare, severe epilepsies that are clinically syndromic. However, two critical questions arise with regard to common epilepsies: First, what is the extent to which these genes may contribute to common epileptic encephalopathies, and second, do rare-occurring mutations — whether inherited or de novo — have large effects on the emergence of seizures, or do common variants with small effect on gene function converge to result in common epilepsies? A report in the Feb. 16 issue of *Lancet Neurology* tackles these questions using exome sequencing in a case-control study of a large seizure cohort, collected through two major consortia funded by the National Institute of Neurological Disorders and Stroke (NINDS) and Epilepsy Research UK.

The study group separately analyzed 640 cases of familial generalized epilepsy, 525 cases of familial idiopathic focal epilepsy, and 622 cases of sporadic non-acquired focal epilepsy. These were compared with data from 3,877 seizure-free control subjects, all of European ancestry. This is the first genome sequencing report of a large case collection of common complex epilepsies. The study focused on ultra-rare DNA sequence variants that occur with a mean allele frequency (MAF) < 0.05% in cases and controls combined. In addition, filtered variants were expected to have a MAF = 0% in the publicly accessible databases of the exome aggregate consortium (ExAC) and the exome variant server (EVS), together totaling more than 65,000 sequences. Through a number of statistical treatments, the authors examined whether the occurrence of loss of function variants (those causing a premature stop in the protein sequence or frame shift loss of function mutations or predicted deleterious amino acid substitutions) occurred more frequently in cases than expected compared with control subjects. A stringent threshold for significance across the study of $P = 8.9 \times 10^{-7}$ was invoked to guard against false positives due to multiple sampling error.

For familial generalized epilepsy, no single gene rose to significance study-wide. However, of the 76,313 variants that fulfilled the selection criteria of ultra-rare, three known epilepsy genes (KCNQ2, GABRG2, and SCN1A) were in the top 10 that were enriched in cases over controls. Intriguingly, 43 known dominant epilepsy genes were over-represented in cases. In the familial focal epilepsy group, DEPDC5 variants reached study-wide significance and another four (LGI1, PCDH19, SCN1A, and GRIN2A) made up the next nearest rank. That five known epilepsy genes should be found as the most highly enriched among this minimally targeted analysis is unlikely to occur by chance. Finally, among the 622 sporadic cases of non-acquired focal epilepsy, no single gene achieved study-wide significance and no enrichment of loss of function/deleterious variants was detected.

■ COMMENTARY

This study is only a beginning for genomic investigation into complex epilepsies, but it provides several important insights. First, genome sequencing can be used in a non-hypothesis-driven approach to discovery of genetic factors contributing to epilepsy. Second, rare, and especially ultra-rare or private genetic variants, can be identified as risk factors for complex epileptic encephalopathies. Third, this implies that a precision medicine approach to treatment of common epilepsies may indeed be a fruitful avenue for clinical care in the foreseeable future. Directions for subsequent research no doubt will include collecting sequences on further enlarging case-control cohorts, similar to those that have been mined from schizophrenia cohorts of 50,000 persons or more. As these datasets grow, it will be possible to examine patterns of genetic variant interactions that may identify risk with increasing accuracy. In the not-too-distant future, sequence data sets from the entire genome, not just the coding exons that make up only 2% of the genome, will enable interrogation of the regulatory variations that also may contribute to epilepsy predisposition. Greater knowledge of the genetic underpinnings of each patient's seizure susceptibility will lead to more individualized strategies of anti-epileptic drug selection. ■

CME QUESTIONS

1. **The diagnosis of Creutzfeldt-Jakob disease requires the following findings *except*:**
   a. clinical picture of rapidly progressive dementia.
   b. MRI features of DWI positive cortical ribbon hyperintensity.
   c. EEG with high-amplitude periodic sharp waves.
   d. positive 14-3-3 test on CSF.
   e. positive RT-QuIC test on CSF.
2. **Treatment of PPMS with ocrelizumab resulted in the following benefits?**
   a. Less disability at 12 weeks after treatment compared to placebo
   b. Less disability at 24 weeks after treatment compared to placebo
   c. Improvement in the timed walking test
   d. Both a and b
   e. All of the above
3. **Which of the following is associated with shorter disease duration in those with Lewy body disease (LBD)?**
   a. APOEε4 status
   b. Braak neurofibrillary tangle staging
   c. Diffuse LBD
   d. More frequent neuritic plaques
4. **Hepatitis E virus has been associated with which of the following neurological conditions?**
   a. Guillain-Barré syndrome
   b. Neuralgic amyotrophy
   c. Encephalitis
   d. Meningitis
   e. All the above
5. **EEG reactivity is an established and clearly defined prognostic marker that reliably indicates chances of neurological recovery of comatose patients admitted after severe brain injuries.**
   a. True
   b. False

[IN FUTURE ISSUES]

Updates from International Stroke Conference 2017