HIGHLIGHTS FROM INTERNATIONAL NEUROSCIENCE MEETINGS

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Nabil Biary, MD, FAAN, FACNS.
Department of Neurology, Prince Sultan Military Medical City, Riyadh, Kingdom of Saudi Arabia.

Meeting Highlights

Skin cells express altered proteins that characterize the most common neurodegenerative diseases?
Ildefonso Rodriguez-Leyva1,2 Erika Chi-Ahumada3 Ana L. Galderon-Garcidueñas4 Veronica Medina-Mier4 Sergio Zarazua5 Maria E. Jimenez-Capdeville6
1San Luis Potosi, 2San Luis Potosi, SLP, 3Veracruz, Veracruz, 4San Luis Potosi, SLP, Mexico

Ildefonso Rodriguez-Leyva, MD, Professor of Neurology and Neurophysiology at the University Autónoma de San Luis Potosi in Mexico said “we hypothesized that since skin has the same origin as brain tissue while in the embryo they may also show the same abnormal proteins. This new test offers potential biomarkers that may allow doctors to identify and diagnose this disease earlier on.” Dr. Rodriguez-Leyva and colleagues took skin biopsies from the retroauricular area of 20 people with Alzheimer’s disease (AD), 16 with Parkinson’s disease (PD) and 17 with dementia, and compared them with 12-age-matched healthy controls. Patients with AD and PD had 7 times higher levels of phosphorylated tau than controls. Patients with PD had 8 times higher level of alpha-synuclein than controls. “This procedure could be used to study not only Alzheimer’s and Parkinson’s disease, but also other neurodegenerative diseases.”

Phenytoin is neuroprotective in acute optic neuritis: results of phase 2 randomized controlled trial
Raju Kapoor, MD
National Hospital, London, United Kingdom

Clinical Trials Plenary Session

Dr. Raj Kapoor and his colleagues (National Hospital for Neurology and Neurosurgery in London) randomly selected 86 patients with acute optic neuritis within 2 weeks of symptom onset to receive either phenytoin or a placebo for 3 months. There was 30% less damage to the nerve fiber layer and the volume of the macula was 34% higher than controls. If this finding is confirmed by a large study it could lead to a treatment that may prevent nerve damage and blindness in MS and could help other attacks of MS, serving a major unmet need.
Epidiolex (Cannabidiol) in treatment resistant epilepsy

Orrin Devinsky, MD, FAAN, Joseph Sullivan, Daniel Friedman, MD, Elizabeth Thiele, MD, Eric Marsh, MD, PhD, Linda Laux, MD, Ian Miller, MD, Robert Flamini, MD, Angus Wilfong, MD, Francis Filloux, MD, Matthew Wong, MD, Nicole Tilton, Patricia Bruno, Judith Bluestein, MD, Anup Patel, MD, Maria Roberta Cilio, MD. NYU Epilepsy Center, UCSF Benioff Children’s Hospital, MassGeneral Hospital for Children, Children’s Hospital of Philadelphia, Lurie Children’s Hospital, Miami Children’s Hospital, Pediatric and Adolescent Neurodevelopmental Associates (Atlanta, GA), Texas Children’s Hospital, University of Utah Medical Center, Wake Forest School of Medicine, Nationwide Children’s Hospital, USA

Devinsky et al presented the results of using cannabidiol (CBD) in treatment-resistant epilepsies in approved open-label expanded access program. Etiologies included Dravet and Lennox-Gastaut (LGS) syndromes, as well as over 10 other conditions. The CBD showed reductions in seizure frequency across multiple drug-resistant epilepsy syndromes and seizure types. Controlled trials are indicated to characterized efficacy and safety.

NNZ-2566: a novel, experimental treatment for adolescent and adult females with Rett syndrome

Daniel G. Glaze, MD, Jeffrey Neul, MD, PhD, Alan Percy, MD, FAAN, Tim Feyma, MD, Arthur Beisang, PhD, Alex Yaroshinsky, PhD, George Stoms, Olga Imas, Kenneth Jordan, MD, FAAN, FACP, Phyllis Stein, PhD, Larry Glass, Nancy Jones, PhD, Joseph Horrigan, MD. Houston, TX, USA

Daniel Glaze, MD, Medical Director of the Blue Bird Circle Rett Center at the Baylor College of Medicine in Houston presented results of a phase II, randomized, double-blind, placebo-controlled, in dose-escalation study of NNZ-2566 in 2 cohorts of females between ages 16 and 45 with late-stage Rett syndrome, which previously showed restoration of the loss of long-term potentiation in the hippocampus, enhanced dendritic growth and improved longevity in the animal model study of Rett syndrome. The higher dose of 70 mg/kg exceeded the pre-specified criteria for improvement, demonstrating clinical benefit in 3 of 6 core areas of measurement and no worsening in any core measurement end point. Clinical benefit was also demonstrated in the subject level analysis. “Although improvement occurred with the lower dose, relative to placebo, it did not meet the targets described in the study statistical analysis plan.” Dr. Glaze said. These findings support further study of NNZ-2566 for treatment of Rett syndrome.

Transmission of α-synuclein in Parkinson’s disease: pathogenesis and implications for therapy

Virginia Man-Yee Lee, PhD
University of Pennsylvania, Philadelphia, PA, USA

Frontiers in Neuroscience Plenary Session

Alpha-synuclein is a target of new therapeutic strategies for Parkinson’s disease. “You can block release of alpha-synuclein from bad cells or block uptake of misfolded seeds by healthy cells. You can prevent seeding of the pathology or you can promote degradation of misfolded alpha-synuclein,” said Virginia Man-Yee Lee, PhD, John H. Ware Third Endowed Professor in Alzheimer’s disease research at the University of Pennsylvania, School of Medicine in Philadelphia. Dr. Lee found that the purified protein form of alpha-synuclein could be manipulated in a test tube and readily form fibrils similar to those found in...
Lewy bodies, and in subsequent experimental injection of the fibrils into the dorsal striatum of wild-type mice pathology spread to across many regions of the brain with depletion of neurons on the side of the substantial nigra where alpha-synuclein fibrils were injected. With blocking the uptake of alpha synuclein with Syn 303 (specific monoclonal antibody) fewer lewy body inclusions and more dopamine surviving in treated cells were seen. Dr. Lee was also able to block the transmission of alpha synuclein using Syn 303 as well as Syn 211, a human-specific monoclonal antibody. “Both 211 and 303, when added to pathology in culture was able to reduce synaptic motor neuron death.” “Immunotherapy may provide a therapeutic approach for treatment of Parkinson’s disease and other synucleinopathies,” Dr. Lee concluded.

Topically applied ketoprofen gel (ELS-M11) in the treatment of severe migraine pain
Wolfgang Liedtke, MD, PhD, William Bauer, MD, PhD, FAAN, Susan Walker, Crist Frangakis, PhD, Joel Saper, MD, FAAN
Durham, NC, USA

Wolfgang Liedtke, MD, PhD and colleagues conducted a randomized crossover, double-blind, placebo-controlled study on 42 randomized migraine patients. Ketoprofen gel applied facially bilaterally over the 3 trigeminal divisions significantly provided sustained pain relief from 2-24 hours in 45% of patients versus 15% of placebo headaches. Those patients treated with ketoprofen gel were at least 3 times as likely to experience relief of associated symptoms (nausea, photophobia). The authors concluded this study provides evidence supporting that topical non-steroidal anti-inflammatory therapy can be an effective treatment for acute migraine.

Abuse potential of antiepileptic drugs: A review using the Vigibase™ Pharmacovigilance database
Barry E. Gidal, David Blum
1School of Pharmacy, University of Wisconsin-Madison, 2Sunovion Pharmaceuticals Inc., Marlborough, MA, USA

Carbamazepine (CBZ), Oxicarbazepine (OXC), Lacosaamide (LCM), Pregabalin (PGB) and Eslicarbazepine acetate (ESL) were selected in this analysis based on data available and known scheduling status. The incident rate per 100 patient-years was determined. Exposure was calculated from prescription data in 13 European countries and the assumed mean daily dose of each AED. Potentially abuse-related AES were reported more frequently with LCM and PGB including specific indicators of abuse, such as euphoria and hallucinations. “Pharmacovigilance database are spontaneous reporting, therefore these findings may underestimate the actual incidence of these AEs in the clinic.”

Transcutaneous pCO₂ and seizures in the epilepsy monitoring unit: associations with markers of seizure severity
Derek J. Chong,1 Palak S. Patel,1 Alla Ahmed,1 Nilofer M. Khan,1 Bryan J. Still,2 Evan Marzouk,3 Daniel Friedman,4 Orrin Devinski2
1New York, NY, 2Livingston, NJ, 3Winston-Salem, NC, 4Saratoga Springs, NY, USA

A new technique to indicate risk of SUDEP drawing blood for ABG is the current gold standard for monitoring oxygen and carbon dioxide levels in peri- and post-ictal seizures, the technique is invasive and painful as stated by Dr. Derek Chong, MD, Director of EEG and Epilepsy Consult Services at NYU
Langone Medical Center in New York City. In contrast, transcutaneous carbon dioxide partial pressure (TCpCO$_2$) measures CO$_2$ diffusion through the skin. “It correlated better with arterial carbon dioxide than the end-tidal carbon dioxide and may be specifically better during seizures and for prolonged wear in the epilepsy monitoring units,” said Dr. Chong. In retrospective analysis using TCpCO$_2$ recordings that captured 15 seizures in 10 adults, changes were similar to prior studies using continuous EEG monitoring and ABG volumes. “The carbon dioxide and not the oxygen were associated with post-ictal generalized electrographic suppression (PGES) on multivariant analysis and that was pretty strong association,” he said. The stent, seizure duration, seizure type and PGES were directly correlated with the change in TCpCO$_2$ and the result may denote greater severity and duration of seizure activity. After validation of TCpCO$_2$ and end-tidal CO$_2$ during seizure, this new technique may indicates the risk of SUDEP and Dr. Chong and his colleagues plan to use them in the design of a preoxygenation intervention study of PGES in SUDEP. He concluded the ultimate goal of future studies is to limit SUDEP.

**SMN2 splicing modifier RG7800 shows dose-dependent increase of full length SMN2 mRNA in first-in-human study**

Heidemarie Kletzl, PharmD, PhD, Anderas Günther, PhD, Jules Heuberger, Geert Jan Groeneveld, MD, Omar Khwaja, MD, Luca Santarelli, MD, Paulo Fontoura, Irene Gerlach, PhD, Teodorica Bugawan; Christian Czeck, PhD

Basel, Switzerland

RG7800 is in development for treatment of spinal muscular atrophy (SMA) and previously had shown to increase function SMN protein levels in the Δ7 mouse model for SMA. Single oral doses of 0.5-90 mg RG7800 were administered to healthy male subjects, in a single-ascending-dose, placebo-controlled, double blind study conducted in Netherlands. “RG7800 was safe and well tolerated in this first-in-human study in health subjects. Proof of mechanism was demonstrated by the shift in SMN2 alternative splicing toward the production of full length SMN2 mRNA. Safety, PK and PD results of this study fully support further clinical development of RG7800 for treatment of SMA.”