HIGHLIGHTS FROM INTERNATIONAL NEUROSCIENCE MEETINGS

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Plenary Sessions

Kenneth W. Imerman, *MD, MS;* ***J. Douglas Miles,*** *MD, PhD;* ***Ingrid Park,*** *MDCM;* ***Araya Puwanant,*** *MD;* ***Robert B. Daroff,*** *MD.*

Department of Neurology, Case Western Reserve University School of Medicine, and University Hospitals Case Medical Center, Cleveland, Ohio, USA

The 2009 Annual Meeting of the American Academy of Neurology (AAN) was held in Seattle, Washington, April 25-May 2, 2009. The scientific presentations numbered over 2020, of which 370 were from the platform and over 1650 were posters. In the following article, Dr. Shireen Qureshi summarizes the scientific highlights of these numerous presentations, each of which has a published abstract in ***Neurology*** 2009; 72: Suppl 3: A1-A608. In addition, Plenary Sessions were held for selected platform presentations, which had no published abstracts. We selected 4 of particular interest, to summarize.

Induced Pluripotent Stem Cells from a patient with Spinal Muscular Atrophy: Implications for Neurology
Clive Svendsen, PhD.

Animal models of human diseases are helpful, but are limited by differences between animal and human biology. Induced pluripotent stem (iPS) cells, which are similar in many ways to embryonic stem cells - but less controversial - can be derived in vitro from human adult somatic tissues, and may provide a way to model human neurologic diseases. In his presentation to the AAN, Dr. Svendsen referred to his recently published article in Nature.[1] He described how his group generated iPS cells from fibroblasts from a patient with spinal muscular atrophy (SMA). For comparison, they also generated non-SMA iPS cell lines. In both SMA and non-SMA cell lines, motor neurons were generated after approximately 4 weeks of differentiation, and with time, the SMA iPS cultures showed a reduction in motor neurons compared to the non-SMA cultures. Patient-specific iPS cells have been created from patients with other diseases, including ALS, but unlike the SMA study, none of these cell lines have shown any disease-specific changes. Potential uses of these cell lines include disease modeling and the screening of potential drug therapies. Dr. Svendsen believes that iPS cells will eventually be routinely used in medical science. In time, new methods of iPS cell derivation may permit the development of banks of cells that could be used clinically. In closing, Dr. Svendsen commented was that while iPS cells may provide a useful alternative for some areas of research, they are not equivalent to embryonic stem cells and that research using embryonic stem cells should not be abandoned.

[1]Ebert AD, Yu J, Rose FF Jr, Mattis VB, Lorson CL, Thomson JA, & Svendsen CN. Induced pluripotent stem cells from a spinal muscular atrophy patient. *Nature* 2009; 457: 277-280.

Parental Dementia and Alzheimer Disease are Associated with Poorer Memory in Middle Aged Adults: The Framinghman Study
Stephanie Debette, MD, PhD.

This was a study of the offspring of Framingham Study patients with dementia to determine if the offspring had a higher than usual risk of developing dementia. The Framingham offspring cohort contained 717 patients with dementia. The diagnosis in the offspring was established by a neurologist and through neuropsychological testing. All were evaluated using a 1-1.5T MRI at the University of Davis in California, with specific attention to hippocampal and white matter volume. Statistical analysis looked at specific interactions that included APOE e4 genes, age of onset, and gender in both parent and offspring? The study found that 281 (39%) offspring had one or more parents with dementia. The mean age of diagnosis in the offspring was 54. The only significant statistical correlation between demented parent and demented offspring was associated with the APOE e4 gene. Brain volume, level of education, and gender had no significant correlation. Offspring of parents with the APOE e4 gene were 4.3 times more likely to develop dementia than those whose demented parents did not have the gene.

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Evidence and the Effective Clinical Neurologist
Louis R. Caplan, MD, FAAN.

"Evidence-based medicine (EBM)" has become a shibboleth. Devotees define acceptable evidence as that derived solely from the results of randomized, controlled, double-blinded trials (RCTs), and urge that all treatment be based on these results. But how should this new EBM concept of treatment be integrated into every day patient care, and how can we add the advances of EBM without losing the true values of the traditional neurological approach to the care of patients? The traditional neurological approach is focused on individual patients and emphasizes making a detailed clinical and differential diagnosis. The diagnosis is based on a thorough history, physical, and neurological examinations, imaging, and laboratory analysis. It is also necessary to determine the severity of the problems, analyze co-morbidities and risk factors, and becoming knowledgeable of the socio-economic-psychological milieu of the patients and their families. Treatment decisions involve weighing and discussing the risks and benefits of all applicable therapies, and discussing these with patients and the families. Evidence-based medicine is an approach to group oriented medicine that makes decisions based on trials, guidelines, and studies. This approach searches for trials and Cochrane reviews, and then follows the guidelines based on RCTs. Physicians who follow this approach are obliged to spend more time on the computer than with patients and families. Moreover, there are several major limitations and problems associated with such trials. The more that diverse subgroups are lumped together, the less specific the results become for individual patients. Some conditions are not sufficiently frequent, such as non-bacterial endocarditis, to allow definitive trial studies. In addition, trials always include extensive inclusion and exclusion criteria, so that often 5-10 patients must be screened for each patient finally entered. Trials may exclude patients who are too ill, too old, too young, too complex, too full of coexisting diseases, women of childbearing age, and those who will not give informed consent. But these are type of patients often seen by neurologists on a daily basis. There have, however, been many useful trials where the patients have been well evaluated with adequate numbers and power, and the situations and treatments studied in the trials are readily applicable to individual patients. These include carotid surgery trials (NASCET, ECST), atrial fibrillation trials, PROACT II, and EC/IC bypass trials. There have also been several trials that have not been as useful, such as trials of antiplatelet or neuroprotective agents in pooled groups of heterogeneous, incompletely studied patients with TIAs or minor strokes. And there have been flawed trials, such as IST and IST3. The risk of fully embracing EBM Guidelines is that payers, managed care organizations, and hospitals may refuse to cover treatments not based on RCTs, and lawyers may sue if EBM based treatments are not used. Patients and physicians may be denied access to non-EBM based treatments and investigations (especially imaging) designed to make specific diagnosis. Dr. Caplan suggests that 1) we must not deemphasize the methods of traditional clinical neurology; 2) we need to integrate the important information from RCTs that is relevant to individual patients into care of that patient; 3) we should utilized all evidence available when considering treatment, not just RCT results; 4) we need to design and perform better trials that more closely mimic patient care and construct better guidelines that are not slavishly limited to results of RCTs; 5) flexibility and context should be included within the guidelines; 6) time is best spent with the patients and family, not predominantly with the computer; 7) we weigh the benefits versus the risks of each potential treatment for the patient's specific problem; and 8) lastly, we curb the insufferable arrogance of the EBM devotees, their constant call for another RCT for everything, and their disdain for any other evidence or opinions. Therapeutic decisions must be made with, by, and for, complex individuals. They cannot be readily homogenized without losing the essence of being an "effective clinical neurologist."

Sudden Unexplained Death in Epilepsy
Elizabeth Donner, MD, FRCPC.

Patients with epilepsy face a greater risk of death than the general population. The Standard Mortality Ratio for epilepsy is 1.4, and children with epilepsy face a 5.3-13 times higher risk of death. The death may be either unrelated to the epilepsy; related to the cause of the epilepsy, such as tumor or degenerative disease; or be a direct result of the seizure itself, as is the case in status epilepticus, traumatic injury, drowning, or SUDEP (Sudden Unexplained Death in Epilepsy). For the term SUDEP to apply, one must rule out documented status epilepticus, traumatic death or drowning, and the post-mortem exam must eliminate toxicological or anatomical causes of death. The death may, or may not, be witnessed. Sudden death is 24 times more likely in the epileptic than the non-epileptic population. In children, SUDEP accounts for 34% of sudden death. Depending on the cohort, the incidence ranges between 0.2-9.3 per 1000 person-years. Due to underreporting from lack of awareness, and low autopsy rate in suspected cases, these values may under-represent the truth. The risk of SUDEP increases with increased frequency of generalized tonic-clonic seizures, duration of epilepsy, younger age of epilepsy onset, and polypharmacy, with anti-epileptic drugs (AED); the odds ratio is 8.1 for 3 or more AEDs versus one AED. The causes of SUDEP are poorly

understood. Most patients are found dead in bed in a prone position, with at least half having had a recent prior seizure. The current model is that SUDEP is preceded by an apneic/hypoxic event or cardiac arrhythmia associated with cerebral shutdown. Areas of inquiry include a possible genetic predisposition, the effect of long-standing seizure disorders on autonomic function, medication, the necessity of a seizure prior to death, and what seizure characteristics lead to a fatal event. Sudden death that is not attributed to a seizure itself may relate to cardiac factors. In animal models, epileptiform discharges influence blood pressure, cardiac conduction, and rhythm. 0.4% of Epilepsy Monitoring Unit (EMU) admissions experience ictal asystole. Reduced heart rate variability, a marker of reduced vagal activity, is a risk for sudden death and is increased in temporal lobe epilepsy. Ion channel disorders may also play a role. Congenital long-QT syndrome, linked to both potassium and sodium channel mutations, increases the risk for syncope, seizures, and cardiac death. Moreover, a family carrying the voltage gated sodium channel subunit gene (SCN1A) also had familial SUDEP. Respiratory factors may contribute as well. In the EMU, ictal apnea occurs in up to 55% of patients, and hypoxemia is found in up to 35%. In animal models, hypoventilation precedes fatal cardiac arrhythmias, and respiratory arrest following seizures. The SIDS brainstem-serotonin hypothesis, in which a defect in normal brainstem responses prevents infants from responding to homeostatic stressors, may provide an explanation for postictal respiratory depression in SUDEP. Prevention of SUDEP centers on reducing the number of seizures as well as the number of AEDs. Nighttime surveillance, shared sleeping accommodations, frequent checks, and audio monitoring may also provide a modest reduction in risk. The SUDEP task force recommends that neurologists inform epilepsy patients, or their parents, of the increased risk of death from SUDEP, as part of a comprehensive educational program. For higher-risk patients, such knowledge may encourage compliance with AEDs and willingness to consider surgery.

Scientific Presentations

Shireen Qureshi, *MD, FRCPC.*
Consultant Neurologist, Internal Medicine Services Division, Saudi Aramco, Dahran, Kingdom of Saudi Arabia

Stroke Highlights

* Federal Drug Administration (FDA) approval of extending EPA for acute treatment window up to 4.5 hours based on the ECASS III study.[1]
  [1]Hacke W, Kaste M, Bluhmki E, Brozman M, Dávalos A, Guidetti D, et al Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. ***N Engl J Med*** 2008; 359: 1317-1329.

* More compelling evidence on the benefit of early endarterectomy (within 2 weeks) in moderately severe stenosis for secondary stroke prevention.

* Establishment of stratification of stroke risk in atrial fibrillation by Hart et al,[2] based on the CHADS2 point system with one point given each for congestive heart failure, hypertension, age >75, and diabetes mellitus, with 2 points for prior stroke/transient ischemic attack, increased evidence for comparative benefit of anticoagulation versus antiplatelet.
  [2]Hart RG, Pearce LA. Current Status of Stroke Risk Stratification in Patients With Atrial Fibrillation. ***Stroke*** 2009; 40: 2607-2610.

Multiple Sclerosis Highlights

* Recent years have witnessed renewed and intensified interest in the complex genetics of multiple sclerosis. Advances in pharmogenetics and pharmacogenomics have led to investigation therapies tackling multitudes of modalities of therapies.

* Natazilamab has been FDA approved in the last 2 years, a promising new modulating therapy despite some serious cautionary side-effects.

* A combination of interferon with glatiramer acetate (copaxone) (called combi-treatment), an NIH supported trial currently in phase III appears promising and provides (proof of principle) therapy.

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* Senetol phase II and phase III trials of various monoclonal antibodies approved by FDA for different diseases such as non-Hodgkin's lymphoma, systemic lupus erythematosus, rheumatoid arthritis, or renal transplant showing good results in select MS patients. These include rituximab, alemtuzumab, ocrelizumab, and daclizumab.

* Oral agents like fingolimod have initially shown improved reduction in relapse rate against interferon, but serious side-effects have halted its release and further phase III studies both in Europe and North America are underway.

* Other oral agents, such as Fumarates (BG0012), laquinomid, teriflunomide, oral adhesion molecule inhibitors (Dirucotide) are under phase II-III studies.

* Immunosuppression by hemato-politic stem cell transplantation offers immuno-ablation and again surely promising benefits in select patients, still more widespread multi-enteric trials are needed.

Epilepsy Highlights

* New guidelines for epilepsy in women and during pregnancy were discussed. Highly recommend avoidance of valproate in pregnancy and in women within childbearing age, due to substantial risk of cognitive impairment along with neuronal tube birth defects in their offspring. Lamotrigine was the most favorable drug in terms of effects on fetuses.

* Monitoring levels was highly recommended in nursing mothers on lamotrigine, carbamazepine, and phenytoin.

* Re-emphasis was made on continuing women on their anti-epileptic medications during pregnancy.

Headache Highlights

* In the field of headache, increasing evidence is being established on the role of anti-convulsants as neuromodulators in migraine prevention.

* For acute migraine management, the calcitonin gene-related peptide (CGRP) receptor antagonist (Olcegepant) is shown to be effective in its intravenous form. A published randomized placebo controlled trial[3] of Tonabersat have been studied with promising results and are comparable to other triptans favorably, lacking vaso-constrictive properties.
[3]Goadsby PJ, Ferrari MD, Csanyi A, Olesen J, Mills JG; Tonabersat TON-01-05 Study Group. Randomized, double-blind, placebo-controlled, proof-of-concept study of the cortical spreading depression inhibiting agent tonabersat in migraine prophylaxis. ***Cephalalgia*** 2009; 29: 742-750.

* Vanilloid receptor antagonist and nitric oxide (NO) production blockage is also in the future domains of migraine treatment.

Neuromuscular Disease Highlights

* More established evidence of usefulness of musk-positive testing for atypical presentations of myasthenia gravis with prominent bulbar and respiratory symptoms.

* Newer treatments, such as steroid-sparing and immunosuppressants, like tacrolimus/FK 506, rituximab, and etanercept are being studied in this field with some promising results.