The AAN remains one of the most widely attended international meetings with attendees reaching up to 5,000, and was held in New Orleans last spring. It had all the aspects of general and speciality neurology topics widely presented. The conference was geared to all levels of audience from medical students interested in the field of neurology, neurology resident trainees, to the highest levels of basic neuroscientists and clinicians. Numerous presentations as parallel sessions, plenary sessions, poster sessions, and workshops were conducted. Below are some of the scientific highlights from the meeting.

Meeting Highlights

Headache


Objective: To provide updated evidence-based recommendations for the preventive treatment of migraine headache. The clinical question addressed was: What pharmacologic therapies are proven effective for migraine prevention?

Methods: The authors analyzed published studies from June 1999 to May 2009 using a structured review process to classify the evidence relative to the efficacy of various medications available in the United States for migraine prevention.

Results and Recommendations: The author panel reviewed 284 abstracts, which ultimately yielded 29 Class I or Class II articles that are reviewed herein. Divalproex sodium, sodium valproate, topiramate, metoprolol, propranolol, and timolol are effective for migraine prevention and should be offered to patients with migraine to reduce migraine attack frequency and severity (Level A). Frovatriptan is effective for prevention of menstrual migraine (Level A). Lamotrigine is ineffective for migraine prevention (Level A).


Stroke

Vascular contributions to cognitive impairment and dementia: a new guidance statement from the American Heart Association & American Stroke Association

Alzheimer’s disease (AD) and vascular cognitive impairment (VCI) were once thought to be distinct entities with little in the way of mechanistic similarity. In the new AHA/ASA guidance statement, we define VCI in the general following manner: A syndrome whereby there is evidence of clinical stroke or subclinical vascular brain injury and cognitive impairment affecting at least one cognitive domain. It is now believed that the entity of mild cognitive
Impairment exists in relation to VCI and that this state may be reversible. Diagnostic criteria for dementia the following features must be met: 1. There is decline in cognitive function from a prior baseline and a deficit in performance in two or more cognitive domains that are of sufficient severity to affect the subjects’ activities of daily living; 2. The diagnosis of dementia must be based on cognitive testing, and a minimum of 4 cognitive domains should be assessed: executive/attention, memory, language, and visuospatial functions; and 3. Deficits in activities of daily living are independent of motor/sensory sequelae of the vascular event.


**Inclusion of stroke in cardiovascular risk prediction instruments: a statement for healthcare professionals from the American Heart Association/American Stroke Association.**

Patients with atherosclerotic stroke should be included among those deemed to be at high risk (≥20% over 10 years) of further atherosclerotic coronary events. Inclusion of nonatherosclerotic stroke subtypes remains less certain. For the purposes of primary prevention, ischemic stroke should be included among cardiovascular disease outcomes in absolute risk assessment algorithms. The inclusion of atherosclerotic ischemic stroke as a high-risk condition and the inclusion of ischemic stroke more broadly as an outcome will likely have important implications for prevention of cardiovascular disease, because the number of patients considered to be at high risk would grow substantially.


**Epilepsy**

**Brain stimulation for epilepsy**

Two major trials were recently published on brain stimulation for epilepsy. The first one involved bilateral stimulation of the anterior nucleus of the thalamus (SANTE) for refractory multifocal seizures. This showed a modest but significant improvement in seizure frequency (40% decrease vs 14%) during the blinded phase (half randomized to stimulation off). The 50% responder rate improved over time: 43% at 1 year, 54% at 2 years, and 67% at 3 years. Overall seizure severity and quality of life improved at 1 year (but no control group for this). Safety was good, though there was some subjective worsening of mood and memory in the active stimulation arm (no objective differences on testing). The second brain stimulation study utilized the responsive neurostimulation system (RNS), in which the device only stimulates in response to an EEG pattern. This device is placed at the seizure focus or two foci; there are 2 leads (subdural or depth) and 8 contacts. It records the EEG and is programmed to detect that patient’s abnormal activity, then stimulate around that area to prevent propagation and to prevent a clinical seizure. Results were similar to SANTE, with modest but significant improvement in the blinded phase, then further improvement over time, with a 43% responder rate at 1 year, 46% at 2 years and >50% responder rate at 4 years. There were improvements in quality of life, including on scales involving memory and attention. Safety was quite good overall with no unexpected issues.


**The ERSET Trial**

In March 2012, the results of the Early Surgical Therapy for Drug-Resistant Temporal Lobe Epilepsy Trial (ERSET) were published in JAMA. Thirty-eight patients with refractory temporal lobe epilepsy (failed two medications) for less than two years were randomized to early surgery (anteromedial temporal resection; AMTR) vs additional
medication trials. 11/15 were seizure free at one year after surgery vs. 0/23 in the medical arm (p<0.001). Quality of life improved more in the surgical patients than in the non-surgical ones. The trial was stopped early due to slow accrual (initial goal was 200 patients). They concluded that “this study support the conclusions of the American Academy of Neurology to refer patients for surgery if full fill criteria and fail anti epileptic meds.


Multiple Sclerosis

Diagnostic criteria

Establishment of diagnosis criteria of primary progressive MS according to the International Panel (Polman 2011) are as follows: 1. One year of disease progression (retrospectively or prospectively determined) 2. PLUS two out of the three following criteria: a. Evidence for DIS in the brain based on ≥ 1 T2+ lesions in at least 1 area characteristic for MS (periventricular, juxtacortical or infratentorial). However, when the patient has a brainstem or spinal cord syndrome, all symptomatic lesions must be excluded from consideration. b. Evidence for DIS in the spinal cord based on ≥ 2 T2+ lesions in the cord. c. Positive CSF (isoelectric focusing evidence of oligoclonal bands and/or elevated IgG index).


Combination therapy

The most obvious combination therapy for MS, and one holding great interest for neurologists, is that which pairs GA with an interferon. After the successful completion of a pilot trial to examine the safety of the combination of weekly intramuscular interferon beta-1a and GA (serial MRIs showed no increased activity in the combination treated patients) (Tullman and Lublin 2005), a very large Phase III trial (called CombiRx), supported by the NIH with additional support in kind by the pharmaceutical companies, has been conducted. This trial enrolled more than 1000 patients and included three groups. One quarter of the patients received GA alone, one quarter received weekly interferon beta-1a alone, and half received the combination of the interferon and GA. Patients were followed for three years in double-blind treatment. The study was powered not only to assess the effect of the combination, but also to provide an answer about the relative efficacy of weekly interferon beta-1a alone compared to GA alone.


Potential future therapy

Alemtuzumab. The monoclonal antibody alemtuzumab (Campath-1H), by targeting the CD52 antigen present on T and B cells and macrophages, causes a sustained depletion of T-cells (Coles et al 1999). Although preliminary trials in the early ‘90s in secondary progressive MS (SPMS) showed discouraging results, subsequent open label trials in severe RRMS were more promising. Based on these results a Phase II head-to-head trial of alemtuzumab vs. subcutaneous interferon beta-1a (Rebif) was initiated.


Daclizumab. Daclizumab (DAC), yet another monoclonal antibody, is directed against the alpha chain (CD25), a component of the high-affinity IL-2 receptor, which is involved in lymphocyte activation. The agent is currently
FDA approved only for use to prevent renal allograft rejection. The drug showed promise in preliminary trials in animals with EAE and in small human trials.


**Fumarate (BG00012).** Fumaric acid esters are oral agents with both anti-inflammatory and potential neuroprotective effects. Two Phase 3 trials, DEFINE and CONFIRM, have now been completed. Results of the former were presented at ECTRIMS/ACTRIMS in October 2011 (Gold et al 2011). A dose of 240 mg of BG-12 was administered either two or three times a day and both doses demonstrated comparable and highly statistically significant benefit compared to placebo. The primary endpoint in this trial was the cumulative probability of relapse and the bid and tid doses had hazard ratios of 0.51 and 0.50 respectively. Annualized relapse rate reductions of 53% and 48% respectively were achieved. Statistically significant benefit of 12-week confirmed progression also occurred with hazard ratios of 0.62 and 0.66, respectively. The number of gadolinium enhanced lesions was reduced by 90% and 73% for the two doses and new or newly enlarging T2 hyperintense lesions by 85% and 74%.


**Teriflunomide.** Teriflunomide, another oral immunomodulator, is a metabolite of leflunomide, which is widely used in the treatment of rheumatoid arthritis. It exerts its effect by inhibiting pyrimidine synthesis in T cells and other rapidly dividing cell populations. Following completion of a Phase II trial that met its primary endpoint of reduction in MRI disease activity, a series of Phase III trials were undertaken. Results of a large randomized placebo-controlled trial have been published (O’Connor et al 2011). Both 7 and 14 mg doses achieved significant reductions in annualized relapse rate of more than 31% compared to placebo. Relative risk reductions of 23.7% and 29.8% in 12-week confirmed disability progression were achieved for the low and high doses, respectively, but only the latter achieved statistical significance.


**Neurointervention**

**New stent retrievers for intra-arterial treatment of acute ischemic stroke**

Results from two studies of these devices were presented at the AHA/ASA International Stroke Conference in February 2012. The TREVO study was a multi-center, prospective, single-arm trial evaluating mechanical thrombectomy with the Trevo System. Patients with persistent large vessel occlusion aged 18-85 with an NIHSS of 8-30 were included. Patients were required to be treated within 8 hours from symptom onset. The TREVO study is a single arm study demonstrating clot removal and received FDA approval by this mechanism based on the results of single arm trials demonstrating clot removal with no controls. The SWIFT study was designed to demonstrate the non-inferiority of SOLITAIRE device compared with a legally marketed device, the MERCI Retrieval System. It was a multicenter randomized controlled trial with blinded primary endpoint ascertainment. Key entry criteria were age 22-85; NIHSS 8-29; within 8h of onset. The SOLITAIRE Study demonstrates superiority of this device over the currently available MERCI device both for clot removal and for clinical outcome. While this would seem to establish clinical benefit, it is well to remember that these results cannot establish the clinical efficacy of

[HIGHLIGHTS FROM INTERNATIONAL NEUROSCIENCE MEETINGS]

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this device without first proving that the Merci device causes no harm, an unwarranted assumption for a device associated with a 9% rate of symptomatic intracerebral hemorrhage and a 38% 90 day mortality. Until there are intention-to-treat clinical trial data demonstrating benefit, it is not possible to select patients for whom the possible benefits of mechanical clot extraction with any device outweigh the risks.


Autoimmunity and newly defined syndromes

Anti-NMDA receptor encephalitis syndrome
The anti-NMDA receptor encephalitis syndrome is quite distinctive. This typically presents in young women (mean 23 y.o.; 93% female) with prodromal fever, psychiatric symptoms, then rapid progression to seizures, cognitive abnormalities, orofacial dyskinesias, autonomic instability and central hypoventilation requiring respiratory support. Many of these patients have ovarian teratomas and dramatically improve if those are resected. Treatment is tumor removal if it can be found (not all are ovarian) and immunotherapy, and many patients recover fully despite being critically ill for some time. In patients with cryptogenic epilepsy, 5/19 tested positive for this antibody in one series. This was associated with psychiatric symptoms and CSF pleocytosis. Only one patient had a neoplasm (multiple endocrine neoplasia, including the ovaries). This entity has been recently described and published in Lancet was specially mentioned at AAN highlights.


Limbic encephalitis
Limbic encephalitis associated with antibodies to the voltage gated potassium channel complex (LE-VGKC) has become more clearly defined. This syndrome consists of behavioral changes, cognitive decline, seizures, and often hyponatremia, and is usually autoimmune and not paraneoplastic. The antibodies thought to be directed against the potassium channel turn out to be directed against related molecules, mainly LGI-1, and sometimes Caspr-2. Most recently, there is a distinctive type of spell associated with this syndrome that appears to be fairly specific for it. These have been termed “faciobrachial dystonic seizures”, and consist of brief tonic spasms lasting only a few seconds, typically involving the face and one hand. These spells tend to precede the rest of the syndrome and can thus be very useful for early diagnosis if recognized. They are refractory to most antiepileptic drugs, but respond well to steroids. So far these occur in non-paraneoplastic cases only.
