

Medical Update Memo

Research News from American Academy of Neurology Meeting, April 9 -16, 2005

Neurologists and neuroscientists from around the world gathered to share their research findings at the American Academy of Neurology's 57th Annual Meeting in Miami, April 9-16, 2005. Following are selected highlights from nearly 200 presentations that had relevance to multiple sclerosis.

During the meeting, the 2005 John Dystel Prize for Multiple Sclerosis Research was awarded to Professor Jack Antel, MD, of McGill University. Dr. Antel was honoured for his major contributions in establishing the study of interactions between the immune system and the brain and its application to MS, and for his role as a leading MS clinician and investigator. One aspect of his work is described below under "Clues to Tissue Damage and Repair."

Spotlight on Pediatric MS

Several presentations highlighted research on children and adolescents who have MS, a population that has not been well studied. Though MS is relatively rare in children, there are an estimated 10,000 persons under the age of 18 who have definite MS and another 15,000 who have symptoms suggestive of the disease. Following are among the results reported in this area:

- ♦ Dr. Brenda Banwell (Hospital for Sick Children, Toronto) and colleagues described the clinical features and outcomes of 36 children, aged 2.2 to 17.8, who experienced an episode of optic neuritis (inflammation of the optic nerve that frequently is the first symptom of MS). They found that visual recovery was excellent, occurring in 89%. To date, 33% have been diagnosed with MS. MS was more likely to occur in children who developed optic neuritis symptoms in both eyes, and whose MRI scans showed disease activity in the brain.

- Two studies attempted to assess the safety of drug therapy by reviewing the medical and laboratory records of children with MS under the age of 18. Dr. Silvia Tenenbaum and colleagues (Hospital de Pediatría Dr. J. P. Garrahan, Buenos Aires, Argentina) reviewed records of 43 children who had received one or more injections of Betaseron® (interferon beta-1b) and were treated for an average of 30 months. There were no serious adverse events recorded. Liver function tests were abnormal in 7 out of 33 children with available information, but were comparable to findings in adults with MS. One child discontinued treatment due to injection site pain. Dr. Daniela Pohl (Georg-August-University Goettingen, Germany) and colleagues reviewed records of 51 children who had been treated with Rebif® (interferon beta-1a) for an average of 1.8 years. Most children started at a dose of 22 mcg, which was increased to 44 mcg if disease activity increased. Two children experienced serious adverse events that resolved when therapy was discontinued; these included a systemic reaction involving general swelling, weakness and fatigue, and in another case, depression. Other side effects were similar to those described for adults. Although these studies provide some information on treating pediatric MS, establishing the safety and effectiveness of MS therapies for children will require larger, controlled clinical trials of longer duration.
- Dr. William S. MacAllister and colleagues (National Pediatric MS Center at the State University of New York at Stony Brook) found that early identification of cognitive problems is crucial in pediatric MS. They administered neuropsychological tests to 37 children with MS, and found that 13 had some cognitive impairment. Importantly, they found that cognitive problems were "predicted" by increases in disease activity. The group encourages physicians who treat children with MS to monitor cognitive function over time, so that interventions can be provided to minimize the effects on children's school life.

During the AAN meeting, the international Pediatric MS Work Group met. This group is developing definitions and diagnostic criteria specific to children with MS, which they hope to test in the future. They are also working to focus the attention of clinicians and researchers on this underserved population.

Clues to Tissue Damage and Repair

This year's winner of the John Dystel Prize for MS Research, Dr. Jack Antel (McGill University), presented findings from his team's ongoing efforts to understand factors that may impede the repair of nerve-insulating myelin damaged by the immune attack in MS. One report focused on a substance known as glutamate, which can over-excite brain cells and may play a toxic role in tissue injury during the course of MS. His team examined progenitor, or immature, cells that

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reside in brain tissue and have the capability of maturing into myelin-making cells called oligodendrocytes. Examining progenitor cells grown in lab dishes, his team found that there is only a short but critical period when these progenitor cells have docking sites, or receptors, for glutamate, which would make them vulnerable to its toxic effects during that period. That period is when the progenitors are in the process of maturing into myelin-making cells but are not yet fully grown. This may make them particularly vulnerable to glutamate damage just when the brain is attempting to develop replacement cells to repair myelin injured in MS.

The MS Scientific Research Foundation awarded \$2.25 million to Drs. Antel, Samuel Weiss and Moses Rodriguez for a continuation of this ground-breaking myelin repair research. For more information, click on [myelin repair project](#).

Imaging Tools for Tracking MS

Magnetic resonance imaging and its high-tech cousins offer researchers non-invasive ways of watching MS activity in the brain and spinal cord, and promise better ways of determining the effectiveness of present and future therapies.

- ◆ Dr. Jack H. Simon (University of Colorado Health Sciences Center, Denver, CO) reported on his National MS Society-funded efforts to examine degeneration of nerve "tracts" (bundles of wire-like nerve fibres). His team is using novel technology called "streamtube diffusion tractography," which involves an advanced form of imaging that measures the diffusion, or flow, of fluids through tissue, and then combines images of several slices of tissue to produce a 3-dimensional map. This novel strategy allowed Dr. Simon to trace and identify tracts that extended through areas of highly active MS lesions (patches of myelin damage or disease activity). Though these tracts looked normal, they are considered "tracts at risk" for future degeneration because of the part that extends through the lesion. Further research may refine this technology so that it will be useful for tracking the disease course and the success of therapies in people with MS.
- ◆ Researchers have been searching for ways to predict disability or brain atrophy (shrinkage) by observing MS lesions that show up in MRI scans. A small study by Dr. Nancy Richert and colleagues (NIH's National Institute of Neurological Disorders and Stroke) looked back on the outcomes of 19 individuals with MS who had had monthly MRI scans taken for an extended period of time, ranging from 3 to 9 years. The investigators reported that the types of lesion that were most predictive of future atrophy were so-called enhancing lesions (patches of active inflammation that show up when the person has been injected with gadolinium, a substance that brightens active lesions on the scan). The more

enhancing lesions a person had had over the years, the more their brains showed signs of atrophy. They also found that available disease-modifying agents that could reduce the accumulation of enhancing lesions slowed the rate of brain atrophy.

- Dr. Richard Rudick (Cleveland Clinic) and colleagues have been following 31 individuals with relapsing-remitting MS over 13 years. They found that T2 lesions, which are fairly stable and not necessarily indicators of active inflammation, were linked to future atrophy. The volume of accumulated T2 lesions, measured early in the course of the disease, correlated with later brain atrophy, especially in older individuals.

Further research on brain atrophy in MS should shed further light on this important topic.

Incidence and Prevalence of MS in Nova Scotia

Dr. Virender Bhan and colleagues from Dalhousie University presented a poster on the incidence and prevalence of MS in Nova Scotia. The investigators used the Dalhousie MS Research Unit database and the Nova Scotia Department of Health Care Administrative databases. Only clinically definite and laboratory supported MS cases were included from the Dalhousie MS Research Unit. Department of Health Care cases had to receive a diagnosis of MS on at least two separate occasions by a neurologist. The investigators reported an MS prevalence rate of 206 per 100,000 in 2001, which is among the highest known in Canada and worldwide. The mean annual incidence rate (number of new cases) was 10.81 per 100,000, which is also high. They suggest the high incidence and prevalence rates likely reflect good case-ascertainment and plan to conduct additional epidemiological studies.

AVP-923 for Laughing, Crying Spells in MS

Dr. Hillel Panitch (University of Vermont College of Medicine, Burlington) reported results from Avanir Pharmaceuticals' multi-center, Phase III clinical trial of AVP-923 (an oral drug combining dextromethorphan and quinidine sulfate) for treating "pseudobulbar affect," a socially disabling condition involving uncontrollable laughing and/or crying that affects a small proportion of persons with MS. Among 150 people with MS and this symptom who were randomized to receive either AVP-923 or placebo for 12 weeks, people receiving the study drug had a greater reduction in scores on a tool that measures pseudobulbar affect and in the number of laughing and crying episodes, and a significantly greater increase in quality of life and relationships. The drug was well tolerated, with dizziness being observed more frequently in the group taking AVP-923. According to a press release, the company has plans of submitting a new drug application for AVP-923 to the U.S. Food and Drug Administration.

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Early Drug Studies

Researchers presented several reports on drugs in the early stages of clinical research; larger studies are needed to further explore the potential results of these agents:

- ♦ In a small, controlled safety study, Dr. Lloyd H. Kasper (Dartmouth Medical School, Lebanon, NH) and colleagues administered one under-the-skin injection of an antibody to the inflammatory protein IL-12p40, or placebo, to 20 people with relapsing MS and observed the groups for 16 weeks. This preliminary study suggested the drug did not cause increased disease activity and may warrant further investigation as a potential therapy for MS.
- ♦ In a small, controlled clinical trial funded in part by the National MS Society, Dr. Dennis Bourdette (Oregon Health & Science University) and colleagues administered ginkgo biloba (an extract made from leaves of the ginkgo tree) or inactive placebo to 39 individuals with MS and cognitive impairment for 12 weeks. A battery of neuropsychological tests was conducted before and after the study to determine any changes in cognitive function. There was a significant difference between the groups on the Stroop Test, which measures learning and memory, with the ginkgo group improving and the placebo group remaining unchanged. There were no significant differences between groups on other tests, and no significant side-effects reported. The investigators suggest that further study of ginkgo biloba for improving attention in MS is warranted.

These and many other studies presented at this meeting testify to the growing breadth and pace of research into multiple sclerosis. Follow-up to these studies will help shape efforts to find new and better treatments and hopefully, a way to restore function in those with MS.

(Adapted from National MS Society (USA) reports)

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