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WORLD NEUROLOGY

THE OFFICIAL NEWSLETTER OF THE WORLD FEDERATION OF NEUROLOGY

A Blueprint for Continuity and Change

BY VLADIMIR HACHINSKI, M.D.
President, WFN

Life is brain. It enables quality of life and human progress. Without a healthy brain, little else matters. The World Federation of Neurology (WFN) aims to integrate, prioritize, and help apply advances in brain diseases and the promotion of brain health worldwide. The best way to ensure this WFN role and future is to help shape it. Continuity without questioning risks obsolescence, and aimless change produces "big thunder, little rain," according to a Chinese proverb. The best time to plan change is during stable evolution.

The history of the WFN has been one of steady progress, particularly in the past 4 years under the leadership of Johan Aarli. Upon meeting him, he strikes one as "a gentleman and a scholar." He is dignified without being pompous, and informal without being familiar. His learning in the arts, literature, and different cultures is impressive, and his manner engaging. His presidency has been enhanced and complemented by his gracious wife Gullborg, who makes everyone feel welcome and at ease.

COURTESY BLANKA JORDANOV

Dr. Vladimir Hachinski, the new President of the WFN, is shown here in front of a flowchart depicting his organizational plan.

When Johan became President of the WFN, I discovered other qualities—his ability for careful planning and decisive action. I was impressed by how thoroughly he planned his tenure, how he identified some difficult problems, and how quickly and decisively he moved to resolve them. Members of his team were encouraged to propose and discuss issues, but there was never any doubt as to who made the final decisions. He has great moral authority through the silent eloquence of his example. He fostered a wonderful team spirit which, in part, explains why the past 4 years were so remarkable.

Among his major accomplishments have been the Africa Initiative; welcoming as a member the Chinese Neurological Society, the world's largest, and several others to take membership up to a record 110 societies; and moving to a 2-year cycle for the world congresses to allow us to take neurology to those who cannot afford intercontinental travel. Johan, a heartfelt thank you!

Some positions have changed, but most of the team remains in place and will build on what has been achieved. The pace of progress needs to be accelerated further if we are to help stem the growing burden of neurological disorders. Already, they are the leading cause of disability adjusted years in the world and they are projected to rise.

Our agenda is huge, and our resources are modest, so we need to integrate, focus, and

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INSIDE

Implant Short-Circuits Some Epileptic Seizures

BY DIANA MAHONEY
Elsevier Global Medical News

BOSTON — Patients with treatment-resistant epilepsy can significantly reduce their frequency of seizures with the use of an implantable device that detects preseizure electrical activity and preemptively aborts seizures.

In a multicenter randomized controlled trial, 191 patients with medically intractable partial onset seizures were implanted with the neurostimulator, and their seizures declined by a mean of 29% during active stimulation with the device, compared with a 14% reduction during sham activation, Dr. Martha J. Morrell reported at the annual meeting of the American Epilepsy Society.

In the later, open-label phase of the study in which all of the patients received the active stimulation, nearly half of the 171 patients for whom 12 weeks of data were available experienced at least a 50% reduction in seizure frequency relative to baseline, said Dr. Morrell, clinical professor of neurology at Stanford (Calif.) University and chief medical officer of NeuroPace, developer of the Responsive Neurostimulator System (RNS).

The cranially implanted RNS device differs from conventional, "open loop" brain stimulation technologies that involve the scheduled delivery of electrical stimulation to specific brain regions independent of brain activity.

"The RNS delivers stimulation in response to a detected event," said Dr. Morrell, noting that the treatment is "individualized and dynamic" in that it uses computer technology to recognize and respond to patterns of brain activity specific to individual patients' seizure patterns.

The responsive neurostimu-

See **Seizures** • *page 8*

EDITOR IN CHIEF'S COLUMN

BY MARK HALLETT, M.D.

An Opportunity to Join The Global Community

In this issue, the WFN Junior Travelling Fellowship program for 2010 is announced. We also have reports from a number of fellows who took advantage of this program in 2009 (see p. 10). This is clearly a fine program, and young neurologists from low or lower-middle income countries should be encouraged to apply.

The first impression after reading over the fellow reports is the sense of enjoyment. Going to these large international meetings gives the fellows a sense of being part of a large enterprise. They see persons giving lectures that they have only read about, they can learn about new techniques for diagnosis and treatment. They seem keen to employ their new knowledge in their home environment. Many of them are also participating in research activities and have an opportunity to present their findings and discuss their work with other interested participants and experts. This is also a critical experience in keeping them motivated and increasing the quality of their work.

It is also a great opportunity, of course, to travel and to experience a new city and country. There is a big difference and a great distance between Addis Ababa and Florence. Interactions with neurologists from many places are important too. All this likely helps to increase understanding and friendship in a world where opportunities to connect are improving but risks still abound because of a residual lack of trust and cooperation between people. ■

2010 Junior Travelling Fellowships

This year, the World Federation of Neurology is again offering Junior Travelling Fellowships for 20 young neurologists from countries that have been classified by the World Bank as low- or lower-middle income to attend approved international meetings.

Applicants should hold a post that is not above that of associate professor and they should be no older than 42 years.

They are asked to send:

- ► The name and dates of the meeting for which they wish to register;
- ► A CV and bibliography;
- ► A letter of recommendation from the head of their department; and
- ► An estimate of expenses, to a maximum £1,000.

Those who are planning to present a paper or poster at the meeting they plan to attend should also include an abstract with their application.

The applications should be:

- ► sent to World Federation of Neurology, Hill House, Heron Square, Richmond, Surrey, TW9 1EP, United Kingdom;
- ► e-mailed to info@wfneurology.org; or
- ► faxed to +44 (0) 208-439-9499.

They should be received at the WFN office by Friday, March 19, 2010. The fellowship awards will be announced soon thereafter. ■

Research Group Holds PD Course at Bali Meeting

BY DANIEL TRUONG, M.D.

Together with the Indonesian Neurological Association, the World Federation of Neurology Research Group on Parkinsonism and Related Disorders organized a course in Parkinsonism and movement disorders in Bali, Indonesia, in November.

It ran concurrent with the annual meeting of the Indonesian association and was an initiative to reach out to developing countries spearheaded by me at the request of Erik Wolters (the Netherlands), the chair of the Research Group.

The faculty included experts such as Roongroj Bhidayasiri (Thailand), Mark Hallett, Katie Kompoliti, Irene Litvan, David Riley, and myself, all of us from the U.S.A., and Erik Wolters (the Netherlands). Topics included Parkinson disease and its management, dystonia, tremor, progressive supra- nuclear palsy, multiple system atrophy, myoclonus, and chorea. As part of the program, 250 textbooks on movement disorders were distributed.

The faculty was impressed with participants' enthusiasm as reflected in the vibrant discussions. Faculty members were also able to meet local neurologists as well as visit the University Hospital of Denpasar. ■

Dr. Truong *is head of the Parkinson and Movement Disorder Institute at Orange Coast Memorial Hospital in Fountain Valley, Calif., U.S.A., which he founded and where he practices as a neurologist.*

Nominations for WFN Medals

The WFN medals—for service to international neurology and scientific achievement in neurology—will next be presented at the 20th World Congress of Neurology in Marrakesh, Morocco, in 2011.

Nominations for these prestigious awards are now invited from WFN members, seconded by at least five neurologists, three of whom should be from other WFN member societies. The nominee should have given his or her consent to the nomination, and a citation of no more than 300 words in support of the nomination should accompany the proposal. Each award also carries an honorarium of $5,000.

Nominations must be marked for the attention of the Medal Committee, and sent c/o the WFN, Hill House, Heron Square, Richmond, Surrey, TW9 1EP, United Kingdom; e-mailed to info@wfneurology. org; or faxed, +44 (0) 208-439-9499. They should arrive at the WFN London Office by April 16, 2010. ■

World Neurology

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FAREWELL NOTE

Facing the Challenges of a New Decade

BY JOHAN A. AARLI, M.D.

As the newly elected President of the World Federation of Neurology, Vladimir Hachinski is leading us into a new decade; there is a worldwide and increasing need for more and better neurological services. The new leadership is exceptionally well positioned to meet these challenges.

Stroke is one of the many global health problems in which the voice of the WFN will be heard. One of the first research projects in the WFN was the compilation of a geographical pathology of cerebral vascular disease in 1957. And stroke has never been more important than now. The main mission of the WFN today is to reduce the global burden associated with all neurological disorders—a burden borne by people everywhere and of all ages and every segment of society. It is the disproportion between the global burden associated with neurological disorders and the available resources to deal with this burden that present a challenge for the WFN.

A Solid Leadership

Let me take this opportunity to thank Dr. Hachinski, Dr. Raad Shakir, the Secretary-Treasurer General of the WFN, and Prof. Werner Hacke, Dr. Ryuji Kaji, Dr. Niphon Poungvarin, Dr. Gustavo Roman, Dr. Roger Rosenberg, and Dr. Marianne de Visser for their efforts and collaboration during the last 4 years. The WFN leadership is solid in its unanimous support to establish high-quality neurological services worldwide. My warm thanks also to the London-based WFN administration, led by Mr. Keith Newton, for its institutional memory, enduring loyalty, and hard work.

Global Links

The WFN has a close collaboration with regional neurological associations. We are deeply indebted to the American Academy of Neurology for its central role in international neurology training in the form of the AAN–CME (continuous medical education) program, which is given for free to developing countries. We have also had the pleasure to be joined by the European Federation of Neurological Societies (EFNS) in executing the Africa Initiative, which we started in 2006. The EFNS has established an important training program in neurology for sub-Saharan Africa, alternating between French- and English-speaking countries

Two neurologists are especially important for the Africa Initiative—Alfred K. Njamnshi from Cameroon, the Pan-African Regional Director, and Amadou Gallo Diop from Senegal, who coined the phrase, "With Africa, For Africa." This has become the theme for the 20th World Congress of Neurology in Marrakesh, Morocco, in 2011, which will be the first WCN on the African continent. The Pan Arab Union of Neurological Societies (PAUNS) has offered training programs in neurology for candidates from sub-Saharan Africa, and the constructive support Dr. Riadh Gouider, the president of PAUNS, is important for our educational activities.

The Asian-Oceanian region has the greatest part of the world's population and has become an important part of the world's neurological research and practice. To acknowledge this strategic position, we organized the WFN Council of Delegates for 2008 in New Delhi, during the 12th Asian Oceanian Congress of Neurology. The WFN is also grateful to the Thai organizers of the 19th World Congress of Neurology, which took place in Bangkok in October and was highly successful.

During my presidency, I had the pleasure of attending the 12th Pan-American Congress of Neurology in Santo Domingo, Dominican Republic, and I was struck by the extent and depth of the neurological activities presented. The experiences from some Central American countries, presented by Dr. Ted Munsat, professor emeritus in neurology at the Tufts University School of Medicine in Boston, and Dr. Marco Medina, director of the neurology training program at the National Autonomous University of Honduras, Tegucigalpa, have been helpful in formulating the Africa Initiative.

Continuing Progress

It is also time to thank the administration at the World Health Organization's Department of Mental Health for its close collaboration and insight and understanding of neurological aspects of public health, which we regard as essential for the development of neurology.

The nucleus of the WFN is composed of the national delegates, and I thank you all for your loyalty to the organization, your engagement, and your collaboration. Our committees—Constitution & Bye-Laws, Africa, Education, Finance, Fundraising, Membership, Nominating, Public Relations, Publications & Website, Research, Stroke Affairs and Liaison, and WCN Liaison—consist of our members and are crucial for the Federation's work and progress.

The new leadership will start the new decade with new committees. Let me thank the committee chairs and members for their engagement in WFN activities and for their hard work, and I give my best wishes to those who will now pick up the torch and carry on the work for world neurology: *Quod bonum felix faustumque sit!* (Cicero)—May it be good, fortunate, and prosperous! ■

Eager Response to Sudan's First Clinical Neurology Course

Sudan is Africa's largest country, extending from the great African Sahara in the north to the equatorial rain forests in the south. Most of its 40 million inhabitants live in the rural areas where farming and animal raising are the main livelihoods. The multi-ethnic, multicultural, and multireligious state is administratively divided into 25 states, with a federal central government based in the capital Khartoum.

Modern medicine was introduced to the country by the British, who ruled the country from 1898 until the independence on Jan. 1, 1956. The Kitchener School of Medicine, which was established in 1923 and incorporated in the University of Khartoum in 1951, has graduated thousands of highly trained doctors. However, neurology has and mostly still is taught to medical students by general physicians. There is no formal postgraduate neurology training program available in Sudan and all of the country's neurologists have been trained abroad. A recent major expansion in the number of medical schools in the country—there are now about 24—has resulted in an unprecedented number of under- and postgraduate students who need training in all the medical specialities, particularly neurology.

With the encouragement and support of my colleagues in Sudan as well as abroad, I was able to arrange and carry out the first formal clinical skills neurology course in Sudan last May at Soba University Hospital, Khartoum, the country's biggest tertiary care university hospital.

BY OSHEIK ABU'ASHA SEIDI, M.B.B.S.

Dr. Seidi is associate professor of medicine and consultant neurologist in the faculty of medicine and Soba University Hospital, University of Khartoum, Sudan.

Registration for the full-day course was limited to 25 candidates, and it was fully booked before we could put a public advertisement. In the end, there were 28 candidates because we also invited 3 senior nurses.

The course began with structured seminars on neurological history taking, clinical examination, localization, and differential diagnosis in neurology. We covered basic neurophysiology and neuropharmacology, held an open discussion forum on epilepsy, and a session on multiple sclerosis supplemented with video material, which the candidates found most useful.

Finally, there was a 2-hour hands-on neurological examination in the Practical Assessment of Clinical Examination Skills format covering a variety of clinical scenarios and common neurological problems in the Sudan. Tutors guided the candidates though examinations of patients with various types of stroke, cerebellar ataxias, peripheral neuropathy, nontraumatic spastic paraplegia, and neuromuscular disorders.

The day ended with a challenging open clinical quiz during which candidates were able to revise the course contents and rehearse some of the procedures. It also included information about conditions that had not been covered in the seminars and clinical examinations.

The course was well received and praised by both candidates and academic officials. Prof. Ammar El Tahir, the dean medicine at Soba University Hospital, Suliman Hussein, the director general of Soba, and Dr. Alaa Hassan Ahmed, head of the department of medicine at the University of Khartoum, attended some of the sessions and left us with very encouraging comments. Feedback from the candidates was also very positive, and they suggested extending the course to 2 days.

We hope we will be able to extend the course to 2 days and that we will be able to attract candidates from the neighboring countries of Kenya, Uganda, Malawi, Tanzania, and Ethiopia.

However, such a course would need a lot of logistic support. The World Federation of Neurology has offered some help, but formal adoption by the WFN or one of its branches would secure its continuity. We would also like to see world-class experts volunteering to teach in upcoming courses. A visit from a representative of the WFN or other international bodies such as the European Federation of Neurological Societies, the American Academy of Neurology, or the Association of British Neurologists, and other African or Arabic neurological societies, would be a major enhancement in helping boost the profile of the course.

In addition to logistic support, we also need tools for neurological examinations, ranging from patellar hammers, ophthalmoscopes, tuning forks, visual acuity and colour vision charts, neuroanatomy demonstration models, to mannequins for training in lumbar puncture.

We also need assistance in establishing a neurology unit at Soba University Hospital as well as devising a program to train 12 epilepsy specialist nurses in the Sudan. ■

Synergy Key to Plan's Success

Contiunity • *from page 1*

leverage improvements in neurological disease and promotion of brain health worldwide. Many opportunities exist for synergy. The Greek root "syn" (with) implies working with others, both individuals and organizations. This includes regional, national, international, and subspecialty groups; the World Health Organization (WHO); and other initiatives with which we can generate synergy, such as the global alliance against chronic diseases. Synergy also implies that the combination is more than the sum of its parts, that is, it creates added value. Value, evaluation, and viability must be our bywords.

Value

If we are to make a difference, we must focus on modest investment, high-yield activities. This usually occurs when there is a great need, a solution, and a big gap between what is known and what is applied. That statement has broad application in neurology. If the WFN concentrates on identifying the minority of actions that yield the majority of results and synergizes with other organizations, then our impact can be many times greater than they would be if we worked alone. The economist Vilfredo Pareto noted in the early 20th century that 20% of people owned 80% of the land in Italy. Years later, the Pareto Principle was reformulated as the 80:20 rule, that is, about 80% of results come from about 20% of the efforts.

Value can also mean "added value." If something is already being done, what else can be done for additional value at low cost? For example, if the WFN cosponsors the teaching of an outstanding individual in a developing country, could the sessions be professionally videotaped, produced, and used elsewhere and on our Web site as part of a growing catalogue of online courses? Or could the production of a short documentary about people from a particular country be used for raising funds and awareness of their needs? Another dimension of value is "comparative value"—what is the value of one activity compared with another?

The American Heart Association, the WFN, the World Stroke Organization, the European Stroke Organization, the European Stroke Conference, the Canadian Stroke Network, the National Institute of Nervous Disease and Stroke, and Lippincott Williams & Wilkins are supporting a synergium (a forum for working together) to develop and commit to a world stroke agenda, identifying in rank order what steps would yield the greatest results. If successful, this process could be a model for developing prioritized agendas for major neurological diseases in cooperation with all relevant organizations.

Evaluation and Viability

A key component of any activity is evaluation. Unless we have objective baseline measures, repeated after implementations, we cannot be sure of our impact. In the era of evidence-based medicine, we need evidence-based actions and evaluations.

Wherever possible, we should look for interconnections and synergies. There are many more worthy projects than we could possibly afford. Thus it becomes critical that we focus our efforts on viability. Before beginning a project, we must ask how it will continue after our involvement ceases. We cannot be a funding agency, so we must harness our true wealth: the prestige, expertise, and commitment of our members.

The WFN is sound academically, administratively, and financially, making this the perfect time to plan change for best results. We can afford "to make haste slowly," *festina lente*, in the words of Augustus. The more we consider, consult, and reflect at the outset, the more decisively and effectively we can move forward.

We will have continuity: Johan has agreed to represent us at the WHO, with whom he published the influential "Atlas: Country Resources for Neurological Disorders" (2004) and "Neurological Disorders: Public Health Priorities" (2006), and to serve as an adviser to the President and the Africa Initiative, his proudest achievement. Secretary-Treasurer General Raad Shakir will continue, with expanded administrative responsibilities and in his influential role as Chair of the Expert Neurology Committee advising on the revision of the International Classification of Disease (ICD-10).

Werner Hacke, now WFN Vice-President, will have the important portfolio of Congresses and will help with our efforts to form alliances with other brain-related organizations. Ryuji Kaji will continue in a new and ambitious portfolio.

We also will have change. Roger Rosenberg, Chair of the Research Committee, ended his tenure after a highly successful scientific and educational program of the 19th World Congress of Neurology in Bangkok, Thailand, organized by Niphon Poungvarin and his colleagues with resounding success. Roger and Niphon, you and your colleagues have set a high standard. Thank you very much!

New Blood

We welcome two new elected trustees, Gustavo Roman and Wolfgang Grisold, both with long-standing involvement with the WFN, Gustavo in neuroepidemiology and Wolfgang in education.

Several other individuals will join the Executive, some with new portfolios. All of the appointments will be for 2 years, renewable, including individual memberships in committees and task forces. This allows for greater numbers of individuals to become actively involved and for flexibility to participate in several activities. Each of the committees will have task forces with specific goals, plans, and timetables.

An important first step is to survey all relevant activities in a given area. For example, a number of different organizations offer a variety of educational activities. Could something be gained by better coordination and a systematic evaluation of quality and results? It would help to know where we are, before we decide where we are going. Many more will be involved and much more will need to be done. Please advise us on ongoing activities and volunteer for specific tasks by writing to info@wfneurology.org.

As Johan has indicated in his farewell message, all Chairs and Committee memberships ceased as of Dec. 31, 2009. The new Chairs are being appointed and with their help, the new committee and task force members. We will aim at an optimal balance between continuity and change as we ask you to join us in broadening the horizons of world neurology. ■

MEETING REPORT

ENS Holds Symposium in India

The 2nd European Neurological Society Symposium in India took place in Chennai in July last year. A panel of four ENS speakers and four Indian neurologists presented a series of lectures and discussed cases with a large audience of more than 400 neurologists from several neurological centers in India.

As president of the ENS, I thanked the organizers for the opportunity to lecture in India and to interact and exchange ideas and experiences with our Indian colleagues. Here is a brief summary of each of the presentations that were made during the 2-day gathering:

► On the first day, I presented a comprehensive review of cerebral venous thrombosis, focusing on several trials and registries that would get underway in the next few years. I urged attendees to consider the participation of Indian neurological centers in the studies.

The next day, I described interventions for increasing the effectiveness of rTPA. I presented a critical review of pharmacological and endovascular interventions—either available or under development—that might overcome the limitations of the 0- to 4.5-hour IV rTPA treatment.

► Dr. Deepak Arjundas, of the department of neurology at the Vijaya Health Centre in Chennai, spoke about stroke in India. He described Vijaya's well-equipped and busy Stroke Centre, though he noted that the high cost of rTPA in India was a barrier for expanding acute stroke treatment.

► Prof. Martin J. Brodie, director of the epilepsy unit at the Western Infirmary in Glasgow, Scotland, reviewed antiepileptic drugs, focusing on their mechanism of action, side effects, and therapeutic spectrum.

He gave a second presentation on the management of epilepsy, using mono- and polytherapy. After his lecture, two Indian neurologists presented two complex clinical cases of epilepsy, which were opened to discussion by the panel and audience members.

BY JOSÉ M. FERRO, M.D., PH.D.

Dr. Ferro is director of the department of neurosciences at the Santa Maria Hospital in Lisbon and chairman of the faculty of medicine at the University of Lisbon. He is president of the European Neurological Society.

► Dr. Roop Gursahani, an epilepsy expert from Mumbai, outlined the clinical effectiveness of leveracetam and reviewed its effectiveness as an add-on therapy, a first-line therapy, and on refractory status epilepticus.

► Prof. Giuseppe Lauria, of the National Neurological Institute and head of the Skin Biopsy, Peripheral Nerve, and Neuropathic Pain Centre in Milan, spoke on painful neuropathy in the context of its pathophysiology, comorbidities, nosological classification, the techniques for diagnosing and quantifying the condition, and available treatments.

► Dr. U.K. Misra, of the department of neurology at the Sanjay Gandhi PGIMS in Lucknow, India, illustrated his talk on peripheral neuropathies with the presentation of several interesting clinical cases, some of them rarely seen in Europe.

► Prof. Alexis Arzimanoglou, of the Institute for Children and Adolescents with Epilepsy at the University Hospitals of Lyon, France, gave a thoughtful presentation of the challenges, advantages, and disadvantages of the classification of epileptic seizures and syndromes. He also delivered the final lecture of the symposium in which he addressed the topic of epilepsy surgery in which he stressed the importance of early surgery in drug-resistant epilepsy and reviewed the presurgical evaluation strategies.

► Dr. V. Jayakumar from Madurai presented a very interesting series of video recordings of different types of seizures in children and adolescents.

At the end of the meeting, we held the final round of the Young Neurologist Excellence Award tournament. The top two competitors won a trip to attend the 2010 ENS meeting in Berlin.

The interest and active participation of Indian neurologists was enormous, and all of the lectures were always followed by numerous and pertinent questions from the audience. In turn, the ENS faculty enjoyed the interaction with their Indian colleagues. ■

XXth WORLD CONGRESS OF NEUROLOGY

With Africa, for Africa

Marrakesh, Morocco, November 12-18, 2011

With Africa, for Africa, **WCN 2011** provides Neurologists in Africa with a unique opportunity to join colleagues from around the world for the largest scientific event in Neurology. **Discover** scientific achievements and interact with delegates of diverse backgrounds and perspectives to find real solutions to improve the long-term outcomes for patients with neurological disorders.

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WFN

SOCIETE MAROCAINE DE NEUROLOGIE

Calendar of International Events

2010

3rd International Conference on Hypertension, Lipids, Diabetes & Stroke Prevention
March 4-6
Berlin
www.kenes.com/strokeprevention

8th World Congress on Brain Injury
March 10-14
Washington, D.C.
www.internationalbrain.org

6th World Congress for NeuroRehabilitation
March 21-25
Vienna
www.wcnr2010.org

2nd International Conference "Advances in Clinical Neuroimmunology"
May 31-June 1
Gdañsk, Poland
www.bokiz.pl/neuroim2010

15th Annual Meeting of the International Society for the History of the Neurosciences
June 15-19
Paris
www.ishn.org

20th Meeting of the European Neurological Society
June 19-23
Berlin
www.congrex.ch/ens2010

14th Congress of the European Federation of Neurological Societies
Sept. 25-28
Geneva
www2.kenes.com/efns2010/Pages/home.aspx

23rd Scientific Meeting of the International Society of Hypertension
Sept. 26-30
Vancouver, Canada
www.VancouverHypertension2010. com

2nd European Headache and Migraine Trust International Congress
Oct. 28-31
Nice, France
www2.kenes.com/ehmtic/Pages/Home.aspx

14th World Pain Clinic Congress & the 1st Asian Congress on Pain
Oct. 28-31
Beijing
www2.kenes.com/wspc/Pages/Home.aspx

2011

10th International Conference on Alzheimer's & Parkinson's Diseases
Mar. 9-13
Barcelona
www.kenes.com/adpd

20th World Congress of Neurology
Nov. 12-18
Marrakesh, Morocco

WFN 2009 ANNUAL REPORT

A Sound Foundation for 2010

BY JOHAN A. AARLI, M.D.

For the World Federation of Neurology, the most important event in 2009 was the 19th World Congress of Neurology, which took place in Bangkok, Thailand, Oct. 24-30.

Despite the international financial crisis and political unrest, the Thai neurologists prepared for Congress in a mature, open, and well-balanced way and made it an extremely successful and memorable conference.

The world congresses in neurology are crucial for the visibility of the WFN and remain the most effective venue for presenting scientific achievements and interaction between delegates of varied backgrounds and perspectives. It is therefore time to extend our sincere thanks to the Thai organizers, and to the WFN officers who were involved in the arrangements for the Bangkok congress.

Dr. Roger Rosenberg and Dr. Naraporn Prayoonwiwat organized the scientific program, Dr. Siwaporn Chankrachang was responsible for the teaching tourses, and Dr. Raad Shakir, with his experience from the world congresses in London (2001) and in Sydney (2005), organized the 3rd Tournament of the Minds. Together with them was an army of hard-working colleagues, each of whom deserves our warm thanks.

Dr. Niphon Poungvarin, the Congress President, and his staff collaborated with the professional meeting organizer, Congrex, to coordinate the lectures, symposia, courses, poster sessions, and exhibitions, as well as the transport between the hotels and congress center. It all was executed in a convincingly effective manner, even in the small details, which gives the Bangkok congress a well-deserved place in the WFN history.

Unique to the WCN 2009 was the presence of H.R.H. Princess Maha Chakri Sirindhorn, who presided over the opening ceremony. Her Royal Highness's presence was a great honor for the Federation, and it demonstrated the Thai Royal Family's broad engagement in science and medicine and in promoting the social and economic development of the Thai nation.

In 2008, the WFN decided to establish two WFN Medals—one for scientific achievement in neurology and the other for service to international neurology. The medals were presented for the first time at the Bangkok world congress. The awardees were Dr. Noshir Wadia of India for his work for service to international neurology, and Dr. Roger Rosenberg of the United States for his scientific achievement in neurology.

At the Council of Delegates, Dr. Vladimir Hachinski was elected President of the WFN; Dr. Werner Hacke, the First Vice-President; and Wolfgang Grisold, a new Trustee. The neurological societies of Albania, Armenia, and Kazakhstan were welcomed as new members of the Federation, which now numbers 110 societies. The Moroccan Neurological Society is already well underway with the preparations for the 20th World Congress of Neurology, which will take place in Marrakesh in November 2011.

An important part of the World Health Organization's international responsibilities is the International Classification of Diseases (ICD). Most countries use the ICD-10, which will now be revised. The WHO Department of Mental Health has appointed a WHO International Advisory Group for the revision of the ICD-10 Chapter VI on Diseases of the Nervous System. The Advisory Group was set up in collaboration with the WFN and had its first meeting in Geneva in June last year. The ICD-11 is scheduled to be completed in 2012.

The Africa Initiative is well established, with Alfred K. Njamnshi (Cameroon) as the Regional Director. Amadou Gallo Diop (Senegal) has put the number of neurologists in sub-Saharan Africa in 2009 at 267. The last estimate, in 1996, counted 121. Even with the inherent uncertainties, the number of neurologists in Africa is increasing, and it is encouraging that new neurologists have now been trained in South Africa for Angola and Namibia. The first Ethiopian neurology residents have completed their training at Addis Ababa University, bringing that country's number of neurologist up to 14—for a population of about 80 million people. The Italian Neurological Society is active in training Ethiopian neurologists.

In 2009, Osheik Seidi organized a neuroscience course in Khartoum, Sudan, and will run another this year. The French Neurological Society has been very active in training African neurologists. Several other national societies are working in various developing countries. National neurological associations can also "adopt" candidates by covering expenses for travel, school, and accommodation for training in candidates from developing countries, provided they return to their own country after they have qualified. Such discussions have already started. ■

People to People Marks Its First Decade

Last year marked the 10th anniversary of People to People, a U.S.-based nonprofit organization that is dedicated to improving the health of Africa's poor, especially those in Ethiopia, and combat HIV/AIDS on the continent.

The group is the brainchild of Dr. Enawgaw Mehari, an Ethiopian-born neurologist who completed his medical training in Czechoslavakia and a fellowship in neurology the United States. After visiting his home country in 1999, Dr. Mehari was moved to motivate those in the diaspora to contribute funds and use their skills in helping make a difference in the lives of those their compatriots.

With funds from donors and the active participation of intellectual, economic, and government leaders in Ethiopia, the organization went from strength to strength in its first decade. It has contributed to the development of a neurology training program, a youth reproductive health program; a knowledge-sharing project in collaboration with the University of Addis Ababa and the World Bank; an international discussion forum on health matters; HIV/AIDS education and awareness programs for high school students; and a boarding school for girls. Other educational initiatives include vocational training for AIDS orphans and a postgraduate program in social work at the University of Addis Ababa.

THE FOCUS WILL CONTINUE TO BE ON MITIGATING THE IMPACT OF THE BRAIN-DRAIN IN THE ETHIOPIAN MEDICAL COMMUNITY.

People to People also publishes the *Horn of Africa Journal of AIDS*, a biannual publication for medical schools in Ethiopia and East Africa and runs a project that posts articles on preventative medicine online for the Ethiopian public. In 2005, it negotiated with Pfizer Foundation for a free supply of the drug fluconazole for AIDS patients with systemic fungal infections.

Looking ahead, the organization remains committed to fostering home-based hospice care in Ethiopia with guidance from U.S.-based hospice professionals and mitigating the impact of the brain-drain among Ethiopian medical doctors and nurses. ■

This article is based on information from People to People.

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NAA Levels Discern MS From Neuromyelitis Optica

BY MICHELE G. SULLIVAN
Elsevier Global Medical News

BANGKOK, THAILAND — Serum levels of *N*-acetyl aspartate are significantly higher in patients with relapsing-remitting multiple sclerosis and clinical syndromes suggestive of MS than they are in patients with neuromyelitis optica and they might be a valid biomarker to help distinguish the disorders.

In a study of 176 subjects, Dr. Carla Tortorella found that serum *N*-acetyl aspartate (NAA) levels were about 14 times higher in those with MS or a clinically isolated syndrome suggestive of MS (CIS) than they were in those with neuromyelitis optica (NMO). In fact, levels in NMO patients were the same as they were in age-matched healthy controls.

NAA is normally synthesized in neural mitochondria and leaves the cell by several methods: passing from neurons to oligodendrocytes where it is catabolized; passing through the astrocytes into the extracellular space and thus into the bloodstream; and passing into the cerebrospinal fluid, Dr. Tortorella said at the World Congress of Neurology. This process is abnormal in patients with MS, leading to increased serum NAA levels, but no studies have compared these levels in patients with MS and those with NMO.

Dr. Tortorella examined serum and CSF levels of NAA in 48 patients with relapsing-remitting MS, 20 with CIS, and 32 with NMO, and included 76 age-matched healthy controls for comparison. At baseline, those with NMO were older (median 43 years) than those with CIS (28 years) or MS (38 years). Disease duration was also different: CIS, 6 months; MS, 6 years; NMO, 5 years.

The Expanded Disability Status Scale (EDSS) score was 1.5 in the CIS group, 2 in the MS group, and 4.6 in the NMO group. None of the MS or CIS patients were taking disease-modifying drugs, whereas 10 of the NMO patients were taking immunosuppressants.

All of the patients submitted serum NAA samples. The levels were similarly high in those with CIS and MS (1.7 mM/L in each group). These were significantly higher than the levels found in those with NMO and in healthy controls (0.12 mM/L each).

All of the MS and CIS patients had CSF levels available for testing, whereas only eight of the NMO patients did, and there were no CSF samples from healthy controls. "Nevertheless, the CSF NAA levels were markedly and consistently higher in the CIS and MS patients [0.68 and 0.76 mM/L] than they were in the NMO patients [0.05 mM/L]," Dr. Tortorella, of the University of Bari, Italy, said.

She found no significant association between NAA levels and age, disease duration, or disease activity. However, in those with MS, she found a significant correlation between increasing NAA levels and worsening EDSS scores.

Because the correlation between serum NAA and MS is so much stronger than it is with NMO, Dr. Tortorella suggested that NAA might be a useful way not only to help distinguish between the disorders but to measure the progression of MS, particularly in the early phase of the disease.

Dr. Tortorella did not have any conflicts of interest to declare. ■

Treatment Individualized

Seizures • *from page 1*

lation system comprises electrodes that are surgically implanted in epileptic regions of the brain and connected to the computerized, battery-powered neurostimulator, which is embedded in the patient's skull. The device, which continuously monitors the electrical activity of the patient's brain, is programmed by a neurologist to detect and disrupt significant electrical events.

"The programming is done wirelessly by the physician via a laptop computer," Dr. Morrell said. "It's highly modifiable in that the physician can view the patient's electrocorticographic activity in real time and change the [signal-detection] criteria at any time based on individual patient characteristics."

Up to two leads, each containing four electrodes, can be connected to the neurostimulator, so the system can monitor and deliver responsive stimulation to two distinct epileptogenic zones independently, she noted.

Because the neurostimulation occurs in response to aberrant electrical activity in the patient's brain, fewer electrical impulses are being delivered to the brain than would occur with continuous stimulation. This in turn diminishes the possibility of treatment-related adverse events, Dr. Morrell explained.

In an initial feasibility study of 65 patients, the responsive neurostimulation system demonstrated excellent safety, tolerability, and preliminary evidence of efficacy, Dr. Morrell said. "There were no serious device-related adverse events, and stimulation-related symptoms experienced by several subjects were addressed by adjusting the stimulation settings."

The preliminary efficacy evidence from that study showed that a minimum 50% reduction in seizure frequency was experienced by 43% of the patients with complex partial seizures and 35% of those with total disabling seizures (Neurotherapeutics 2008;5:68-74).

In the double-blind pivotal trial, the 191 patients were randomized to active or sham therapy. All of the patients were between 18 and 70 years of age (median age 35 years), and all had partial onset epilepsy localized to one or two foci and had failed at least two antiepileptic medications.

The patients were taking an average of three antiepileptic medications to attempt seizure control, and approximately 34% of the patients had been treated previously with vagus nerve stimulation, 33% had prior surgical resection, and 16% had been treated with both.

"These patients tended to be very ill. Most of them had epilepsy for more than 20 years, and many were having at least three seizures per 28-day period—often many more than that," Dr. Morrell said.

Of the 191 patients implanted with the responsive neurostimulator device, 50% had mesial temporal seizure onset, 42% had neocortical seizure onset, and 8% had both, Dr. Morrell said in a press briefing at the meeting.

The trial consisted of an initial, 12-week period prior to system implantation during which baseline seizure activity was collected, followed by a 12-week blinded period when participants were randomly assigned to have the responsive stimulation activated or left inactive, she said.

At each of the 31 trial sites, the patients and one neurologist were blinded to the stimulation status, while a separate neurologist programmed the devices in order to maintain the study blinding. The responsive stimulation was optimized in the treatment over the next 4 weeks, followed by 84 days of data collection. At the end of the blinded efficacy period, stimulation was activated for all of the study participants for 2 years post implantation, Dr. Morrell said.

In addition to the statistically significant reduction in seizure frequency in the active therapy group relative to those in the sham therapy condition, there were no serious, unanticipated device-related adverse events during the trial, nor was there a difference between the two groups with respect to the rate of adverse events, including depression, memory impairment, and anxiety, Dr. Morrell reported.

The findings suggest that responsive neurostimulation may be a promising treatment option for individuals with seizures that are resistant to conventional antiepileptic therapy. It is important to note that the apparent increase in the number of patients experiencing at least a 50% reduction in seizure frequency relative to baseline during the open-label phase of the study suggests that the system might become more effective over time, Dr. Morrell noted.

The responsive neurostimulation system has not yet received approval from the U.S. Food and Drug Administration, but NeuroPace plans to submit a premarket approval application to the agency in early 2010, Dr. Morrell said. ■

VITALS

Major Finding: Seizures declined by a mean of 29% during active stimulation with a neurostimulator over the first 12 weeks, compared with a 14% drop during sham activation.

Data Source: Multicenter, randomized, sham-controlled clinical trial of 191 patients with medically intractable partial onset seizures.

Disclosures: Dr. Morrell is chief medical officer of NeuroPace, which developed the system and funded the trial.

COMMENTS

Risks Offset Improvement

Using neurostimulation for seizure control is not new. In the early 1970s, Dr. Irving S. Cooper and his colleagues demonstrated that cerebellar stimulation was capable of reducing seizure frequency in half of treated patients.

However, this current trial is a customized treatment, where each patient receives the most appropriate type of stimulation possibly designed with our current technology. The study findings will contribute to our understanding of treatment resistance in epilepsy. Is resistance associated with the structure where the seizures arise? Could resistance be associated with specific electrical patterns that are not "aborted" by a safe stimulation? Or is it possible that all types of seizures can be equally controlled in a number of patients receiving neurostimulation, and other factors (such as individual genetic profile) play an important role in resistance to treatment? Further analysis of the results should help clarify these issues.

Some patients may not be too excited about a 40% reduction in seizure frequency. However, in patients with refractory epilepsy, we rarely observe a pharmacologically induced improvement of this magnitude that is sustained past the "honeymoon" period with a new medication. In the few patients who achieve such an improvement, the side effects of the drugs are frequently intolerable.

Therefore, despite the small risks associated with the surgical device implantation, neurostimulation offers the possibility of a significant improvement in seizures without the common side effects of drugs.

DR. DANIELLE M. ANDRADE
is the director of the Transitional Epilepsy Program at the University of Toronto.

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2009 JUNIOR TRAVELLING FELLOWSHIP ROUNDUP

A Chance to Connect, Share, and Learn

9th Congress of the French Neuroscience Society, Bordeaux, France (May 26-29)

BY MOUNIR OUZIR

Making Worthwile Contacts. This 3-day gathering was cochaired by Prof. Abdelhamid Benazzouz and Prof. Stéphane Oliet, both of the University of Bordeaux.

The program comprised 10 plenary lectures, among them the Paul Broca Lecture given by Pierre Magistretti, Ph.D., of Switzerland, titled "Neuron-Glia Metabolic Coupling and Plasticity; and the Alfred Fessard Lecture, delivered by Christine Petit, Ph.D., of France, on linking deafness genes to auditory physiology.

I presented a poster on the impact of lead on the circadian rhythm of locomotor activity and the prophylactic effect of melatonin and 5-metoxytryptophol in rats. The circadian rhythm of locomotor activity and its synchronization by light is an essential behavioral parameter for assessing the function of supply-chain integration of photic information. It is currently known that lead interacts with the glutamatergic transmission, especially by blocking *N*-methyl-D-aspartate receptors.

My colleagues and I studied the impact of lead on the rhythm of circadian activity, knowing that the suprachiasmatic nucleus is the gateway to photic information mobilizing a glutamatergic synapse. Our results showed a decrease in locomotor activity and disturbance of the rhythm of circadian activity in the lead-treated rats, suggesting the deterioration of the transmission of photic information toward the suprachiasmatic nucleus.

Moreover, we found that melatonin and 5-methoxytryptophol seemed to be protective against these effects.

I appreciate the opportunity afforded me by the WFN to attend this Congress. I encountered leading neuroscientists and learned about new developments in technology and research. In addition, I made contact with Prof. Benazzouz, and this year, I am going to be working with him on Parkinson's disease. ■

Mr. Ouzir *is a doctoral student at the Laboratory of Clinical Neuroscience and Mental Health at the University Hassan II in Casablanca, Morocco.*

BY SAMIRA CHAIB

Encouraging Scientific Cooperation. The Bordeaux neuroscience congress was attended by researchers, lecturers, and students working in neuroscience in the public and private sectors.

It was a great opportunity to share recent advances in research that is shaping the understanding of brain mechanisms and the treatment of neurological and psychiatric diseases. I firmly believe that it is such sharing that encourages scientific cooperation.

I presented a poster based on my research work in which I am evaluating the antinociceptive and anti-inflammatory effects of the ethanolic extract of the root of the Moroccan medicinal plant, *Rubia peregrina*.

Many of the sessions I attended were useful and interesting, such as those addressing ethical considerations in the neurosciences, depression in OCD and related disorders, and new concepts in the pathophysiology of pain.

My thanks to the WFN for awarding me the travelling fellowship. It allowed me to attend this inspiring meeting and to discover the charms of Bordeaux, which is classified by UNESCO as a World Heritage Site. ■

Ms. Chaib *is a doctoral student in the Laboratory of Pharmacology, Neurobiology, and Behaviour in the Faculty of Sciences at Cadi Ayyad University in Marrakesh, Morocco.*

13th Congress of the European Federation of Neurological Societies, Florence, Italy (Sept. 12-15)

BY YOHANNES WOUBISHET WOLDEAMANUEL, M.D.

Sharing New Skills. Earlier last year, I met the presidents of the WFN and EFNS in Addis Ababa and became aware of the WFN's mission to develop neurology in Africa, and in sub-Saharan Africa in particular. I was motivated to work toward that goal, which was also echoed at the congress in Florence.

I learned much while I was there and look forward to other opportunities of learning new skills and being able to apply them in the clinical setting and share them with my Ethiopian colleagues.

Numerous talks made an impression on me. Dr. Anna Poggesi of Italy spoke about using the white matter hyperintensities load as a predictor of subcortical vascular encephalopathy, based on preliminary data from the LADIS [Leukoaraiosis and Disability] study. She and her colleagues found that severe age-related white matter changes were associated with the presence of specific neurological signs, independently of infarcts.

In a session on small-vessel diseases it was suggested that an early feature of vascular dementia might be both dysexecutive symptoms and memory decline, rather than one or the other. Poster presentations on neurobrucellosis and on amyotrophic lateral sclerosis in HIV patients, and an analysis on AIDS and leukoaraiosis were all thought-provoking.

Finally, I was fortunate to attend a lecture on mirror neurons and their importance in neurological and psychiatric disorders by Prof. Giacomo Rizzolatti of the University of Parma (Italy), lead investigator of the team that discovered mirror neurons in the macaque monkey.

To the WFN, I say thank you the Italian way: *"Grazie mille!"* ■

Dr. Woldeamanuel *is in the department of neurology at Addis Ababa University, Ethiopia.*

BY MOHAMMED EL-SHERIF, M.D.

Opportunities Abound. Given this volume and range of experts at the EFNS meeting, I learned many new things, made new contacts, and discovered new opportunities.

All of the scientific sessions I attended were interesting, especially one that was titled "The Good Life: Patient Self-Management Arts and Education," that showed how people with neurological illness can achieve a better quality of life through the arts and education.

A series of hands-on teaching courses were particularly informative, especially those that were on electromyography, nerve conduction, and transcranial magnetic stimulation. I already work in electrophysiology but I welcomed the practical reviews and exposure to new information.

I presented a poster on an evaluation of the central nervous system affection in patients with diabetes mellitus that was followed with a lively discussion that provided helpful comments on the work.

Since the meeting, I am more proactive in dealing with my patients, more focused on my teaching and research and on ensuring that I keep up with the latest developments. My deep appreciation goes to the WFN for awarding me the fellowship. ■

Dr. El-Sherif *is an assistant lecturer in the department of neurology at Mansoura University (Egypt).*

19th World Congress of Neurology, Bangkok, Thailand (Oct. 24-30)

BY ANITA ARSOVSKA, M.D.

Exposure to Innovation. The congress theme "Innovation in Neurology," was echoed in each of the presentations in which participants learned about the latest advancements in stroke, epilepsy, multiple sclerosis, movement disorders, headache, and pain.

I gave a poster presentation based on a case report on Sneddon's syndrome, epileptic seizures, and recurrent stroke, which was followed by a useful discussion with my colleagues. I had many similar opportunities to speak to experts in neurology, to share experiences, and exchange ideas.

I was also exposed to a tremendous amount of new information about recent advances in neurology, for example, developments in the new antiepileptic drugs as well as advanced imaging of epilepsies, new treatment options for ischemic stroke, new diagnostic and therapeutic possibilities of neurovascular ultrasound, and the potential therapeutic role of stem cells in neurological diseases. It was the kind of information that I can pass on to my colleagues and students and apply when I treat and diagnose my patients.

I am very thankful to the WFN for this unique opportunity and the generous support that to allowed me to attend the Bangkok congress. ■

Dr. Arsovska *is a specialist-neurologist and teacher at the University Clinic of Neurology, Vodnjanska, Skopje, Macedonia.*

BY AHMED ASHAFUDDOULA, M.D.

Meeting the Experts. It was my great fortune to be able to attend the WCN, and I thank the WFN for the experience of a lifetime.

Being in the presence of renowned neurologists and many other experts was an enriching experience. Their lectures, the presentations of their research works, and the workshops and teaching sessions were invaluable, exposing the participants to the latest advances and developments across the spectrum in neurology and neurological science.

One of the highlights for me was a lecture on carotid endarterectomy by Prof. Hans-Christoph Diener, the pioneer of stroke units in Germany.

I enjoyed sharing my views and knowledge with others during the debate sessions for the poster presentations. In fact, it has encouraged me to possibly present a poster at the next meeting I attend.

Continued on following page

Continued from previous page

The education program on acute stroke therapy and stroke prevention was most useful and informative from a clinical practice perspective. I hope soon to be able to attempt thrombolysis in acute stroke in my country. We use botulinum toxin to treat hemifacial spasm and blepharospasm but not in post-stroke spasticity.

Other sessions on infections of the nervous system, electrophysiology, movement disorders, and slide preparation, were equally informative. ■

DR. ASHAFUDDOULA *is assistant professor of neurology at the SZR Medical College in Bogra, Bangladesh.*

BY RIZALDY PINZON, M.D.

Constructive Participation. The extensive program offered at the WCN offered many opportunities for learning and exchange among the participants.

Within the first 2 days, I had already participated in four workshops. One workshop, on botulinum toxin, was very interesting, and I am eager to use it in my patients in my practice in Indonesia. Another, on testing autonomic disorder, made me realize that autonomic complaints are commonly underdiagnosed and undertreated by neurologists.

It was a unique experience for me to be able to attend so many lectures by leaders in the specialty. One such address was presented by Dr. Vladimir Hachinski, the newly elected president of the WFN. He spoke about stroke and emphasized that the increase in the number of strokes in many parts of the world is the result of urbanization and Westernization. That is most definitely the case in Indonesia, where I practice.

I also found the scientific session on pain and headache interesting and informative. This is a common complaint in our in outpatient clinics, and I was once again intrigued by a report about using botulinum toxin injection for treating migraine.

After the workshops on Sunday, Oct. 25, we attended the opening ceremony where we were entertained with traditional Thai dancing and performance arts and a grand banquet.

This congress was an important and enriching experience for me and I thank the WFN for the fellowship award. ■

DR. PINZON *is in the neurology department at Bethesda Hospital, Yogyakarta, Indonesia.*

BY TRINH THI NGOC TRINH, M.D.

Invaluable, Enriching Experience. My trip to the WCN in Bangkok marked the first time I had traveled abroad to an international scientific meeting. There was such a wide range of useful and excellent sessions that I had to carefully select which I attended.

I attended a session on acute cerebral ischemic stroke that dealt with selection of patients to receive tPA based on penumbral criteria using diffusion- and perfusion-weighted imaging mismatch and transcranial doppler ultrasonography. Another session on stroke provided useful information about trends in antithrombotic therapy.

In particular, I enjoyed the many visual presentations during discussions about neuroimaging and electroencephalography, and especially a series of sleep EEGs and video monitoring that demonstrated differentiation between epileptic and nonepileptic paroxysmal events in diagnosing epilepsy.

Prof. David Zee, of Johns Hopkins University, Baltimore, U.S.A., conducted a course in nystagmus, in which I learnt about pathophysiology, investigations, new treatments and how to approach to patients with nystagmus.

I was able to update my knowledge of differential diagnosis and pathogenesis of restless leg syndrome and the role of iron in RLS, and learned a number of new techniques relating to the diagnosis, treatment and management of narcolepsy and cataplexy. I also benefited from other sessions on movement disorders, multiple sclerosis, and neuropathy.

The talks, seminars, symposia and contributions of medical knowledge in this Congress were invaluable to me. My special thanks to the WFN for making my attendance possible. ■

DR. TRINH *practices as a neurologist in Ho Chi Minh City, Vietnam.*

Testing for Genetic Dementia Presents Ethical Nuances

BY RAQUEL SÁNCHEZ-VALLE, M.D., PH.D., AND ALBERT LLADÓ, M.D., PH.D.

Dr. Sánchez-Valle and Dr. Llado are in the Alzheimer's Disease and Other Cognitive Disorders Unit in the department of neurology at Hospital Clínic in Barcelona.

The prevalence of genetic dementia is about 1% in patients suffering from neurodegenerative dementia, varying from less than 1% in Alzheimer's disease to 10%-15% in frontotemporal lobar degeneration or prion diseases.

Genetic AD is usually associated with autosomal dominant early-onset AD. It resembles early-onset sporadic AD, though some mutations may present particular phenotypes. Causal mutations have been described in three different genes: amyloid precursor protein (APP), presenilin 1 (PSEN1), and presenilin 2 (PSEN2). Mutations in PSEN1, in chromosome 14, are the most frequent and to date, 177 missense mutations have been published (http://www.molgen.ua.ac.be/ADMutations/). APP is located in chromosome 21, and 32 pathogenic missense mutations plus duplications of the entire gene can cause genetic AD. PSEN2 is located in chromosome 1, and 14 pathogenic mutations have been described in this gene.

Genetic frontotemporal lobar degeneration (FTLD) is even more heterogeneous. The first mutation causing FTLD was identified in 1998 in the microtubule-associated protein tau (MAPT) gene, in chromosome 17. Since then, it has been shown that more than 44 missense mutations plus partial deletions of the gene cause the disease. Genetic defects in progranulin (PGRN), also in chromosome 17, were shown to cause FTLD in 2006, but since then, up to 67 point mutations and the complete deletion of the gene have been described in familial FTLD.

MAPT mutations cause autosomal dominant early-onset FTLD with almost complete penetrance by age 65 years. The phenotype of PGRN mutations is more heterogeneous, resembling frontotemporal dementia, progressive aphasia, corticobasal degeneration, or even AD. The disease usually presents as familial dementia, but may also appear as sporadic or late-onset dementia. Less frequently, mutations in chromatin-modifying protein 2B gene (CHMP2 in chromosome 3), valosin-containing protein (VCP in chromosome 9), or TAR DNA binding protein gene (in chromosome 1) cause genetic FTLD.

Genetic prion diseases are associated with missense mutations or insertions in the prion protein gene. Surprisingly, 40% of genetic prion diseases lack familial history of disease. They usually present as rapidly progressive dementia, but may mimic early-onset AD or FTLD. Despite the number of possible genetic defects, no genetic alteration is found in 11% of autosomal dominant early-onset AD, one-third of autosomal dominant FTLD, and in an unknown number of familial poor classified dementia, suggesting new genes causing dementia are yet to be discovered.

However, given the number of analyses that need to be performed to establish if a patient suffers from genetic dementia as well as the low prevalence of genetic cases, genetic studies are too time-consuming, expensive, and inefficient to be done routinely in patients with dementia. Testing is usually restricted to most common genetic defects in those cases with an early-onset autosomal dominant pattern of inheritance. However, different circumstances, such as incomplete penetrance, de novo mutations, or lack of familial information cause genetic dementia to present sometimes without familial history of disease."

Therefore, strict criteria for genetic testing selection could lead to the underdiagnosis of genetic cases. In this sense, research is now focused on markers that could screen more accurately which cases should be genetically tested and which genes should be studied in each case.

To date, levels of the protein progranulin in plasma, serum, or CSF are the only biomarker that is useful in this sense. Pathogenic mutations in PGRN cause disease through loss of function (haploinsufficiency). Some researchers have shown that carriers of PGRN mutations present reduced levels of progranulin in plasma, serum, or CSF, compared with controls or familial noncarriers, with no overlap between values.

In addition, reduced levels of progranulin are seen in all phases of the disease, including presymptomatic individuals. These levels can be measured by an enzyme-linked immunosorbent assay, which is cheaper and easier than direct sequencing of the complete gene. Of course, a low level of progranulin does not predict which genetic defect the patient has in PGRN, but it does avoid having to spend time and money studying cases of PGRN negative familial FTLD, and it allows for the screening of PGRN defects in broader series of dementia to avoid clinical misclassification.

Apart from deciding "when" and "which" genetic testing should be done for dementia, there are two other questions: "what for?" and "hows?" should the testing be done. No different treatments or prognostic clues can be offered to genetic cases. In addition, detecting a genetic abnormality that causes dementia in a patient puts all of his/her direct family members at 50% risk for dementia without any possibility of avoiding or even delaying the disease onset. However, many patients and their relatives request the genetic assessment because they want to establish the cause of the disease for either family or financial planning or simply to know what the future might hold for them. In this sense, the results of genetic counseling programs for dementia show that genetic testing of pathogenic genetic defects is safe even for asymptomatic at-risk subjects when performed by a multidisciplinary trained team with pre- and post-test assessment sessions (Arch. Neurol. 2001;58:1828-31; Am. J. Alzheimers Dis. Other Demen. 2005;20:233-8).

Finally, most cases of dementia are not caused by a concrete genetic defect. Even though, heritability—the extent to which genetic factors explain a phenotype—is calculated to be as high as 60%-80% in sporadic AD. After hundreds of genetic association studies, only the presence of the allele E4 of APOE has been unequivocally established as a genetic risk factor for AD, and it accounts for 50% of the genetic susceptibility for AD in whites.

New technologies, with genomic-wide association studies of thousands of subjects will probably identify new risk factors, such as the very recently described clusterin, PICALM, or CR1 (Nat. Genet. 2009;41:1088-93 [Erratum in: Nat Genet. 2009;41:1156]; Nat. Genet. 2009;41:1094-9). Epidemiological studies of genetic risk factors provide valuable information about the molecular basis of disease. Nevertheless, the management of information about genetic risk factors at the individual level is complex. At the symptomatic level, detection of the APOE E4 or another genetic risk factor may increase the positive predictive value of a particular diagnosis. Even so, the benefit is low and dementia guidelines such as those of the European Federation of Neurological Sciences or the British National Institute for Health and Clinical Excellence do not recommend routine genotyping for clinical purposes.

RESEARCH IS FOCUSED ON MARKERS THAT COULD MORE ACCURATELY SCREEN WHICH CASES SHOULD BE TESTED AND WHICH GENES ARE STUDIED.

At the asymptomatic level, known and to-know genetic risk factors could trace profiles of risk and even calculate the relative risk for the future development of disease. The REVEAL study showed that the disclosure of APOE status in adult children of AD patients is safe (N. Engl. J. Med. 2009;361:245-54). However, if the general population pretest risk for being demented is 1% at age 65 and about 13% at age 85, it is of doubtful clinical interest to know through genetic testing if the risk is higher or lower, when complete or null risk cannot be assured and no prevention strategies could be offered.

Social requests are often different from medical recommendations, and it is not science fiction to predict that genetic risk scanning for cardiovascular diseases, cancer, or dementia will be soon offered to the general population. Technical and ethical issues about management and interpretation of results also will arise in parallel to exciting discoveries in the genetics of dementia, and researchers and clinicians should prepare for such challenges. ■

A Valuable Update on Trends

Neuroscience in Medicine: Third Edition
Edited by P. Michael Conn (New York: Humana Press, 2008)

BY JAGJIT S. CHOPRA, F.R.C.P.E., PH.D., F.A.M.S., F.I.A.N.

Dr. Chopra is a former Editor in Chief of WORLD NEUROLOGY *and currently serves on its Editorial Advisory Board.*

The third edition of this book provides a comprehensive overview of the basics in anatomy, physiology, and medicine and their implications for the practice of neurology.

The 55 authors, all experts in their respective areas of research, have produced an up-to-date, user-friendly volume of work for medical and postgraduate students, nurses, neurologists, and general practitioners who have an interest in neurology and want to review the basic science underlying clinical issues. Among the topics covered are cytology and organization of cell types, anatomy of the spinal cord and brain, the physiology of ion channels, transporters and electrical signaling, synaptic transmission, and presynaptic and postsynaptic receptors.

The subjects of neuroembryology and neurogenesis are presented with great clarity, and details of vasculature of human brain and clinical correlations of stroke are a good example of how the book presents its information, starting with the basics and progressing to clinical applications.

Also emphasized are the functions of the cerebellum, brain stem, and cranial nerves; the trigeminal and limbic systems; basal ganglia; and the thalamus. The basic aspects of pain, visual system, and audition are particularly well explained, as are disorders of language and immunology. The authors also discuss the intricacies of the biology of drug addiction and neuropathology of disease, again from the basics through to clinical application.

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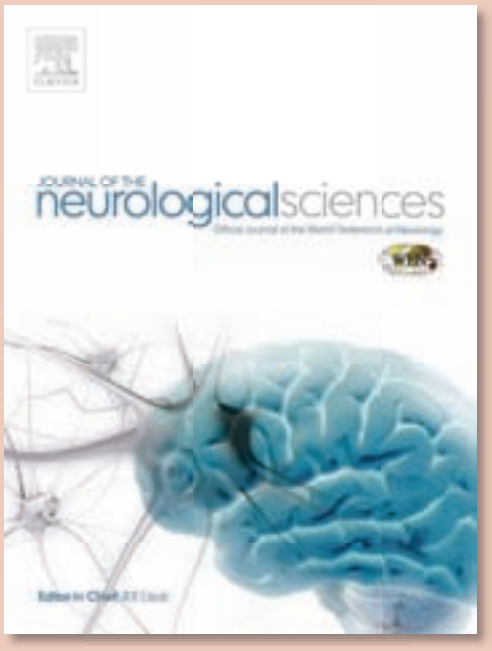

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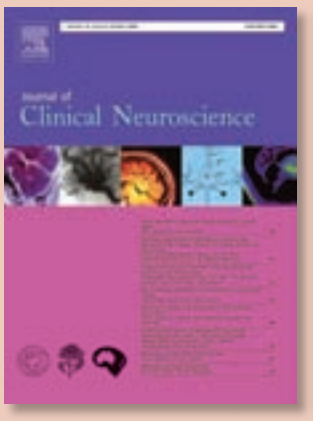

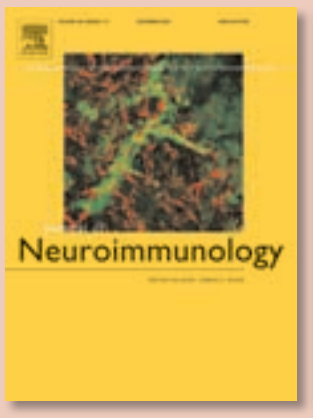

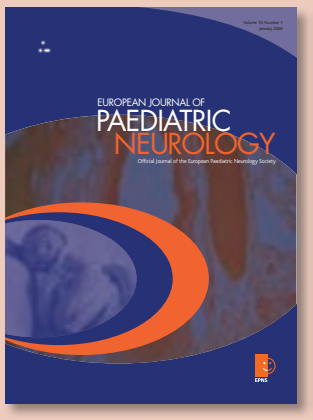

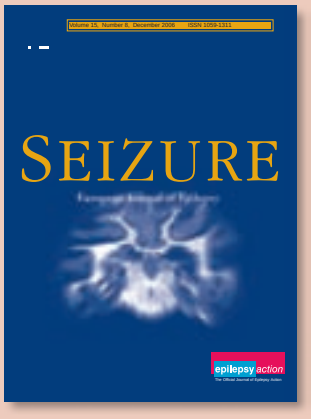

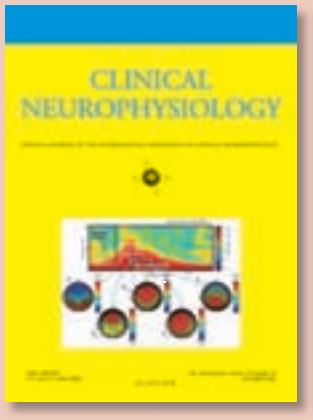

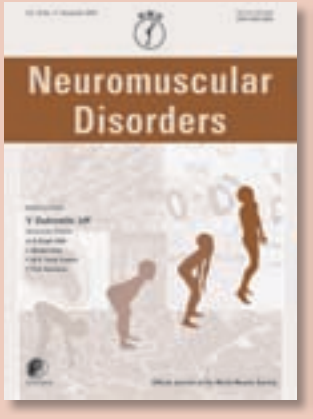

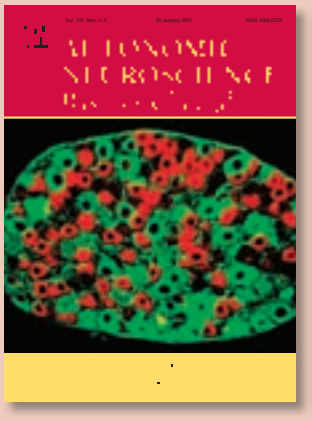

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HIGHLIGHTS FROM THE JOURNAL OF THE NEUROLOGICAL SCIENCES

Atopic Myelitis Seen in Korean Patients

BY ALEX TSELIS, M.D., PH.D.

Spinal cord disease, or myelopathy, can be a diagnostic and therapeutic challenge. The spectrum of causes of myelopathy is broad and includes trauma, nutritional deficiency (such as vitamin B_{12} and copper deficiency), viral infections (HIV and human T-lymphotropics, herpes and West Nile viruses), bacterial infections (*Treponema pallidum*), parasitic infections (schistosomiasis), metabolic diseases (hepatic myelopathy), autoimmune diseases (multiple sclerosis, systemic lupus erythematosus, Sjogren's syndrome, vasculitis), and other inflammatory processes (sarcoidosis). Some of these are quite common; others quite rare. For a substantial proportion, no cause is ever determined.

Myelitis, or inflammatory myelitis, often has an autoimmune or dysimmune basis, although the precise trigger is not usually known. The difficulty is compounded by the fact that most forms of myelitis are clinically very similar and there are few easy clues to the cause. An exception would be the coincidence of weakness and numbness occurring simultaneously with a clear-cut zosteriform rash; the diagnosis is then easily made.

A novel form of myelitis was first described by researchers in Japan in 1997, in which four patients with atopic dermatitis developed a sensory myelopathy, with an increased IgE level in the blood, as well as abnormal signal in the cervical cord (J. Neurol. Sci. 1997;148:199-203).

The IgG index was normal, and there were no oligoclonal bands in the cerebrospinal fluid. The IgE antibodies were directed to mite antigens, and the patients developed this disease at a time of year when the mite population increased in Japan. More Japanese patients were reported in the next few years, a minority of whom had motor manifestations as well. The question arises: Is this emerging myelitis ("atopic myelitis" [AM]) confined to Japan, or is it also present elsewhere in the world?

In the current paper, Dr. In Soo Joo and his colleagues at Ajou University College of Medicine, Suwon, South Korea were able to identify several cases of atopic myelitis in Korea (J. Neurol. Sci. 2009;285:154-8).

Characteristics Echo Those in Japan

The cases were recruited from idiopathic myelitis cases in the Ajou Myelitis Registry database, and of 29 idiopathic cases, 14 had AM with hyperIgEemia and mite-specific antibodies.

The clinical characteristics were very similar to those seen in the Japanese patients, with a relatively benign clinical course and no clear response to intravenous steroids. Comparisons were made between AM and non-AM idiopathic myelitis. AM was primarily sensory, with no or mild weakness, and lasted several months instead of several weeks.

Dr. Joo, the corresponding author, is a full professor at the College of Medicine. He became interested in AM when he started seeing an increasing number of cases similar to those appearing in Japan. He notes that atopic diseases have generally become more common in Korea and seem to be following changes in the environment and diet, possibly mirroring similar changes in atopic diseases elsewhere in the world.

He speculates that AM is more like the opticospinal form of multiple sclerosis (MS) or neuromyelitis optica than the more usual relapsing-remitting MS.

Dr Joo has an interest in neuromuscular and spinal cord diseases, especially amyotrophic lateral sclerosis (ALS), and is involved in designing studies of gene therapy (using stem cells) in treating these diseases. ■

DR. TSELIS *is an associate professor of neurology at Wayne State University in Detroit, U.S.A. He is the book review editor for the Journal of the Neurological Sciences.*

FROM THE PAGES OF THE LANCET NEUROLOGY

Biomarkers Could Flag HD Progression From Premanifest Stage

A series of potential biomarkers of Huntington's disease (HD) might allow for much earlier diagnosis of the disease, improved treatment and monitoring of disease progress, and more reliable end points for therapeutic trials.

Treatments for HD "[lack] sensitive and stable markers of the changes that occur in subjects carrying the HD mutation as they pass from what is currently known as the premanifest stage [when they show no obvious clinical signs of disease] to conventionally diagnosed HD [which relies on clear motor signs being visible] and its progression," said Dr. Sarah Tabrizi, of the Institute of Neurology, University College London.

"[We hope] to confirm the existence of biomarkers of disease progression from the very early premanifest stage; indeed, our work so far confirms that neuronal dysfunction begins many years before [Huntington's disease] is clinically diagnosed," she said.

In their baseline report of what will be a 3-year multinational study, the researchers presented data on 366 individuals: 120 carriers of the HD mutation in the premanifest stage, divided into two groups based on the median number of predicted years (10.8 years) to diagnosis (preHD-A or further from diagnosis, and preHD-B or closer to diagnosis); 123 patients with early HD, divided into two groups based on functional capacity (stage 1 HD or HD1, and stage 2 HD or HD2); and 123 age-matched and sex-matched controls. These different groups provided a range of stages of HD spanning many years (Lancet Neurol. 2009;8:791-801)

All of the participants underwent 3T MRI brain scans and a range of assessments, including recording the horizontal eye position, an isometric force test involving sustained tongue protrusion, a self-paced finger tapping test, gait analysis, cognitive assessment including negative facial emotion recognition, a visual working memory test and smell identification test, and a neuropsychiatric assessment and quality of life evaluation.

Neuronal loss or dysfunction possibly occurs years before a conventional clinical diagnosis.

DR. TABRIZI

"Significant differences were seen between the groups in many of these tests, reflecting progression of the disease," said Dr. Tabrizi. "The results also supported the idea that neuronal dysfunction or loss occurs years before a conventional clinical diagnosis is usually made."

For example, the 3T MRI scans showed a 0.8% reduction in brain volume in the preHD-A group, compared with the controls, progressively rising to 8.5% in the HD2 group. White matter loss and atrophy of the caudate and putamen was evident even in the preHD groups.

Similarly, the variability of tongue force exerted by the preHD-A patients showed a significant deficit, compared with the controls, becoming progressively worse with disease progression (adjusted means per subgroup and confidence interval: controls 3.27 [3.18-3.36], preHD-A 3.46 [3.33-3.58], preHD-B 3.68 [3.55-3.81], HD1 4.32 [4.21-4.43], HD2 4.45 [4.29-4.61]). The same trend was seen for the smell test results, the visual memory results, and the oculomotor antisaccade error rate; problems already present in the preHD-A patients worsened toward the HD2 group.

"The identification of biomarkers is likely to have a major impact on the capacity to perform high-quality clinical trials in HD," commented Anne Rosser, Ph.D., of the University of Wales, Cardiff.

Dr Rosser added that "although the current well-validated battery of semi-quantitative clinical outcome measures have played a critical role in clinical studies to date, they tend to be laborious, time consuming (and thus expensive), and subject to rater variability and considerable noise.

"Biomarkers that track disease progression will substantially increase the power of clinical trials in manifest disease and will make possible trials in presymptomatic patients that would otherwise be impractical due to the very large numbers of subjects and long follow-up required. It is also important to recognize that some biomarkers may provide new insights into the pathogenic processes in HD, an understanding of which is the cornerstone of designing new treatments," Dr. Rosser commented.

Roger Barker, Ph.D., of the University of Cambridge (England), noted that "[it will] be of interest to see how much these markers of disease change over time, how linear these changes are, and the variability of them between different individuals.

"If the more simple markers identified in this study change over time in all patients in a reproducible way, and truly reflect the core pathological events in the disease, then for the first time we have measures by which to look for disease modification with novel therapeutic agents in HD," he continued.

If their potential is borne out by the study's longitudinal results, then these markers could also have an important impact on routine clinical testing for Huntington's disease.

Most of the tests required are inexpensive and easily performed by trained personnel. Many more clinics might therefore be able to conduct them and ultimately provide better care for HD sufferers.

—Adrian Burton

Mr. Burton is a freelance writer for The Lancet Neurology.

NEUROLOGICAL STORY

A Dizzy Concoction of Fugu, Sake—and Haiku

BY JUN KIMURA, M.D.

Dr. Kimura is professor of neurology at the University of Iowa, Iowa City, U.S.A., and professor emeritus, Kyoto University, Japan.

The annual meeting of the Japanese Society of Clinical Neurophysiology was held in Kokura, on Kyushu island, in October 2009. The meeting, organized by the society's president, Prof. Sadatoshi Tsuji, was a great success, as usual, but this time there was a special treat. After a series of superb scientific sessions, we had a welcome banquet as part of typical Japanese hospitality. The local food served included seasonal raw fish, fugu, for which this is the season, and Kyushu is the place.

Now there have been a few reports of fatality associated with eating improperly prepared fugu because of tetrodotoxin, a poison that the fish makes, presumably to scare away its enemies. But these reports have not frightened the Japanese, who consider this a delicacy. However, there was enough concern that the topic of the toxin dominated the conversation. Dr. Hans Lüders, of Case Western University, Cleveland, Ohio, U.S.A., was an invited guest at the meeting, and although he had been a neurology resident at Kyushu University some years ago, he did not know much about the fish, probably because at the time he could not afford it.

Dr. Ryuji Kaji, a WFN trustee, was able to elaborate on the fugu, a funny-faced fish also known as a puffer fish. This most expensive cuisine in Japan could present a risky challenge for a cook who does not know physiology.

According to Ryuji, a self-proclaimed gourmet, fugu is palatable for chewing but tastes bland unless it contains a trace amount of the tetrodotoxin, which is a sodium channel blocker. After the death of a well-known performer of Kabuki (a traditional Japanese form of theater) with this type of poisoning some 35 years ago, the Japanese government tightened the regulations governing the cooking of fugu and the qualifications of the chefs who prepared it to ensure the removal of the liver, which contains the toxin.

A tiny bit of the toxin that escapes, however, makes it a local delicacy, causing a tingling of the tongue and a slight numbness around the mouth while chewing. He concluded that the risk was small at our party, which was attended by physiologists and physicians familiar with the diagnosis and treatment (unless the toxin would kill us all).

Dr. Hiroshi Shibasaki, the President of the International Federation of Clinical Neurophysiology, who is preparing for this year's International Congress of Clinical Neurophysiology in Kobe, Japan, noted that the safest way to proceed is to have one guest eat the fugu first, and then, if he survives for half an hour, the rest of the guests can eat it with less concern. As a matter of pride, of course, if a chef does knock off one of the guests, he must commit suicide.

Ryuji then posed a scientific question. If tetradotoxin blocks the sodium channel, it should cause conduction block of motor and sensory fibers, thus causing paralysis and loss of sensation—not positive signs like tingling. But, no one had a clear explanation and no further scientific exchange ensued as, by then, no one was able to carry on meaningful discussion under the influence of sake.

I had also asked at a local restaurant if it is difficult to remove the toxin for safe consumption. The chef replied: "No, not at all; all you have to do is to get rid of the liver which contains the toxin. Anyone can do this without difficulty." So I asked why we need a licensed cook to do just that. "Because a good cook keeps a piece of liver inside. Some leave one quarter, others, one third, and still others, nearly one half so that you feel a slight tingle when you bite the fish. Trouble is, if it tingles too much, you may not wake up next morning," he replied.

This information inspired Dr. Mark Hallett, another guest at the meeting (and the editor in chief of WORLD NEUROLOGY) to write a haiku, which is a Japanese poem of three lines, with a syllabic structure of 5-7-5:

That was good fugu
My tongue was tingling strongly
Now syounara

Analyzing these verses with his usual critical eye, Hiroshi commented that this was not a proper haiku, which is a serious poem that also must contain something about the seasons. Instead, the poem was a senryu, a more cynical one, usually with a hidden message.

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The puffer fish (fugu) is guaranteed to cause tingles in diners—and perhaps even inspire them to poetry.

Shortly after Mark took over WORLD NEUROLOGY, he created a new column, Neurological Story, and asked me to submit one on any topic of my choice. I said I would think about it, which was a big mistake. He took it to mean "Yes," or so he implies, as all good editors do. Ever since, he has made me feel like I owe him an article every time we meet. I have, therefore, been trying to avoid him. This, however, has proven difficult. With this submission, I have fulfilled my obligation, which has been bothering me for some time. Accepted or rejected, I no longer owe him an article. ■

Editor's note: *I continue to welcome Neurological Stories. If any one can explain the tingling with tetrodotoxin, we would all be grateful. Delivering the answer in the form of a haiku will gain extra credit. Jun, a former WFN president and outstanding scientist and educator, is very busy as a popular lecturer all around the world, and this has inspired another senryu:*

The measure of man
Is not his achievements, but
Frequent flier miles.

Carotid Endarterectomy Deemed Safer Than Stenting

BY KERRI WACHTER
Elsevier Global Medical News

NEW YORK — Carotid endarterectomy was deemed safer than carotid artery stenting for symptomatic patients based on results from a multicenter study of 1,710 patients, although postprocedure complications suggest that as stent technology evolves, the two approaches will need to be revisited.

The International Carotid Stenting Study found there were twice as many strokes (58) for carotid artery stent (CAS) patients in the per-protocol 30-day analysis vs. 27 in the carotid endarterectomy (CEA) patients. Furthermore, 72 CAS patients had a stroke, MI, or had died at 120 days of follow-up vs. 43 (5.1%) in the CEA group, Dr. Frans Moll said at the Veith symposium on vascular medicine sponsored by the U.S.-based Cleveland Clinic.

However, "the complications occurred not so much during [stenting] but at 1-3 days after the procedure," he said in an interview. "This brings me to the conclusion that [perhaps] some technical features of the stent are not yet as good as we wish they were." Perhaps "the development of stent technology has not reached the level necessary to replace traditional surgical skills," said Dr. Moll, a professor of vascular surgery at the University Medical Center in Utrecht, the Netherlands.

In this study, patients with symptomatic carotid artery stenosis greater than 50% were randomized to treatment with CAS (853) or CEA (857). To be included, patients had to be deemed as requiring treatment and the stenosis had to be suitable for both stenting and surgery. Ultrasound study of the carotid artery to be treated was performed at or before randomization and at 1 month following treatment—and will continue annually.

Participating surgeons had to have performed more than 50 CEA or 50 CAS procedures—and more than 10 cases/stents per year—at supervised centers in the study. Several stents were approved for use in this trial. All patients received best medical care including antiplatelet therapy or anticoagulation (as appropriate) and control of medical risk factors. Aspirin plus clopidogrel were provided before stenting.

The researchers were able to analyze the 853 CAS patients and 857 CEA patients by ITT up to 120 days post randomization. The per-protocol analysis included 821 patients in the CEA group and 828 in the CAS group. In terms of secondary outcomes at 120 days more patients in the CAS group had any stroke (65), compared with the CEA group (34). The hazard ratio for any stroke or death for CAS vs. CEA was 1.91.

In an MRI substudy involving 108 CAS patients and 92 CEA patients at five centers, "we see that there is a real difference between CAS and CEA" at up to 6 weeks' follow-up, said Dr. Moll. In terms of new ischemic lesions seen on diffusion-weighted MRI after the procedures, the odds ratio for CAS vs. CEA was 5.24.

"The number of serious strokes was not so much different—disabling strokes were not the biggest difference—but all of these minor strokes and lesions on diffusion-weighted imaging were striking," Dr. Moll said in an interview.

Notably, protection devices were recommended for use during CAS but were not mandatory. A total of 245 patients got CAS without a protection device, and the remainder had protection. There was no significant difference in outcomes regardless of whether a protection device was used, Dr. Moll said. ■

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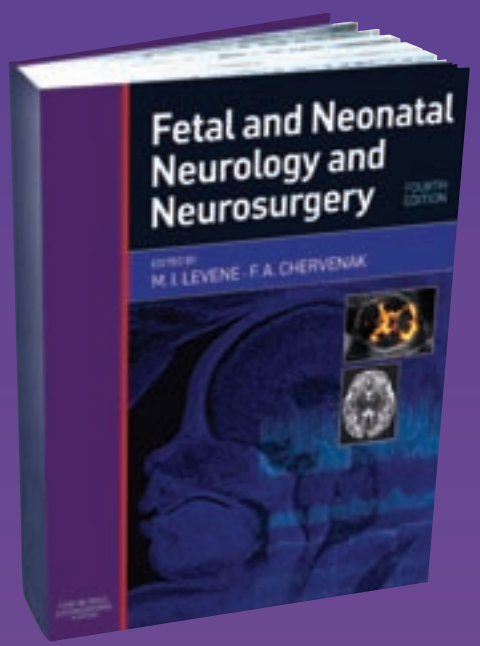

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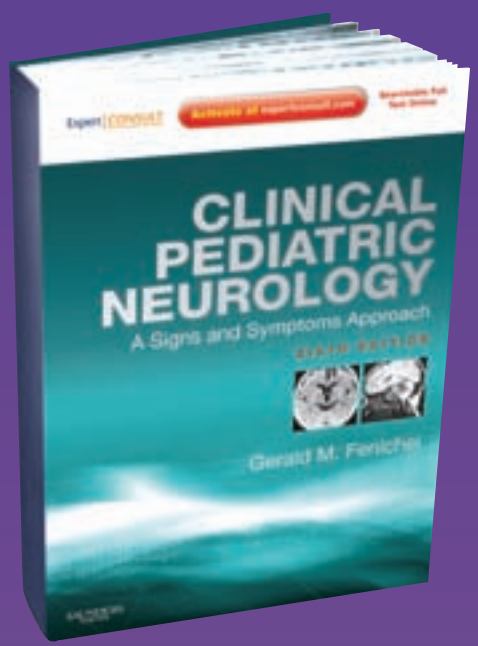

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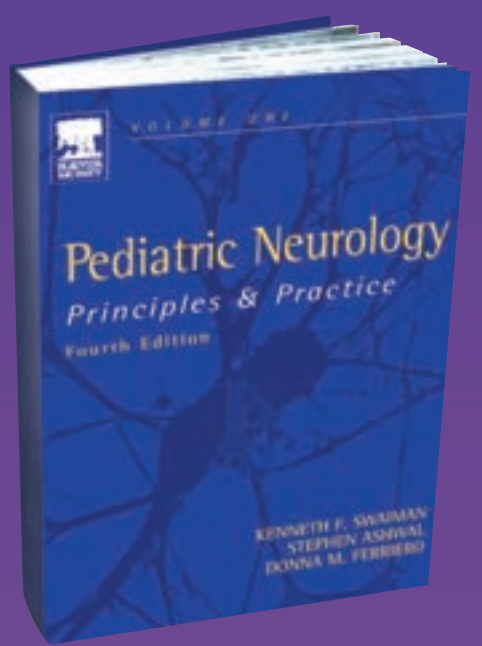

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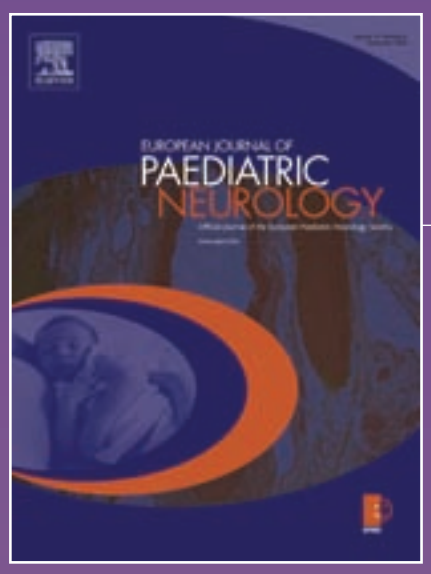

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