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WORLD NEUROLOGY

THE OFFICIAL NEWSLETTER OF THE WORLD FEDERATION OF NEUROLOGY

WFN ELECTIONS 2011

Candidates' Statements for Elected Trustee

GUSTAVO C. ROMÁN, MD

I was born in Bogotá, Colombia, the first-born of a large family of six brothers and three sisters. My father was a veterinarian and my mother a school teacher, and they inspired in us a strong sense of family values and instilled in us the notion that, in the absence of wealth, the only inheritance that we were to receive from them would be a solid education.

My father's legendary clinical accuracy and one of his books, *The Microbe Hunters* by Paul de Kruif (1926), sparked my interest in medicine. I received my medical degree from National University of Colombia, after which my wife Lydia, a classmate and fellow physician, and I obtained scholarships to begin our specialization in Paris.

My lifelong interest on the effects of hypertension, stroke, and heart disease on cognition and mood originated from my participation in a research study on lacunar strokes at La Salpêtrière Hospital, University of Paris, under the mentorship of Prof. Jean-Claude Gautier, Prof. François Lhermitte, and Dr. Raymond Escourolle. Based on this neuropathological study, I wrote a seminal paper on Binswanger disease (JAMA 1987;258:1782-88) that stimulated widespread research on chronic white matter ischemia, a condition also called "leukoaraiosis" by Dr. Vladimir Hachinski, current

See **Román Elections** • *page 6*

JOHN H. WOKKE, MD, PHD

I was born in 1952 in a typical Dutch city with canals and windmills. My father was a young child during the Depression of 1929 and completed only 3 years of primary school education, but he encouraged us to finish our schooling and go on to university. Medicine was a logical choice for me because it seemed to open up so many intriguing opportunities and possibilities. Even as a medical student, my interests in research and teaching were already evident. Histology was my favorite subject and for 2 years, I examined the developing fetal thymus in rats; at the same time, I was also involved in teaching junior students.

In 1978, I graduated with a medical degree from the Free University in Amsterdam, the Netherlands, where I also did part of my training as a neurologist. Sint Lucas Hospital, a regional teaching hospital near Amsterdam, where I was trained, had the country's first CT scan, and when I saw for the first time what was actually happening in the brains of my patients, I knew that we were at the brink of revolutionary changes in neurology. I decided to subspecialize in neuromuscular diseases at the University Medical Center Utrecht under the supervision of Prof. Frans Jennekens, a renowned expert in neuromuscular diseases who

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INSIDE

Infection May Be Culprit in Post-H1N1 Narcolepsy

BY SHARON WORCESTER
Elsevier Global Medical News

The onset of narcolepsy during a 10-year period in China was highly correlated with seasonal and annual patterns of upper airway infections, and was generally independent of H1N1 influenza vaccination, contrary to reports of narcolepsy following H1N1 vaccination in northern Europe and other areas.

Self-reported data on the month and year of narcolepsy onset in 629 patients who were diagnosed between September 1998 and February 2011 indicate that onset is most frequent in April and least frequent in November in this population, with a nearly sevenfold increase from trough to peak, Dr. Fang Han of Peking University People's Hospital, Beijing, and colleagues reported.

A greater-than-threefold increase in narcolepsy onset occurred about 6 months following the 2009 H1N1 winter influenza pandemic, but interviews with 142 patients who recalled whether they were vaccinated against H1N1 revealed that vaccination was not likely related to the increase, because only 8 (5.6%) of the patients reported having been vaccinated, the investigators said (Ann. Neurol. 2011;70:410-7).

Furthermore, about 25% of 150 patients recalled having been sick with an infection within a few months of narcolepsy onset, and 85% of those reported symptoms of upper airway infection, including 2 who reported "flu" and 2 who reported "strep throat."

Animal studies suggest that about 80% of hypocretin/orexin–producing neurons must be lost before symptoms of narcolepsy are exhibited, which could explain the 6-month delay between winter airway infection and narcolepsy onset occurrence, they noted.

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EDITOR IN CHIEF'S COLUMN

A Novel Approach To Research

We all want to bring the best medical care to our patients, and it is pretty clear that diagnostic methods and therapies are constantly improving. Even though it is difficult for the practitioner to keep up to date, I think we can all agree that this is a good thing. There are many aspects of medical research; some certainly seem esoteric and far removed from anything useful, but we need a variety of types of research if we are to continue moving ahead.

MARK HALLETT, MD

My favorite example recently is the rapid development in assessing a person's genome. Currently, if a genetic disorder is suspected, typically the specific mutation is evaluated. An alternative, available even to the public, is an array of several hundred thousand SNPs (single nucleotide polymorphisms). Whole exome analysis is becoming available, and may even be cheaper than assessing several specific mutations. Why not get the whole thing for less? But the whole exome is not really everything – that is the whole genome and even that will be possible in a few years. And, what is possible will eventually move into clinical practice—the question is not "whether," but "when."

Much of the early research requires experimental animals, and such research is constantly under attack. A new novel illustrating both the value of animal research and the threats on it, *Uncaged*, is reviewed by Jasper Daube on page 15 of this issue of World Neurology. His review piqued my interest, so I read the book as well. It is a short novel with some extremes in the story line and stereotyped characters, but fast-paced and engrossing. Could some of the disasters in the book really happen? Could an antibiotic-resistant variant of bubonic plague be an act of terrorism? Not impossible, and maybe this recently almost happened! The book certainly shows how animal research is important.

When you are discussing advances in medicine with your patients, there is value in reminding them about the role and importance of research including animal research. ■

WORLD NEUROLOGY FOUNDATION

Ramachandran Is New President

Dr. Tarakad Ramachandran has been elected President of World Neurology Foundation (WNFo), a body that promotes neurological care and education in countries in need and supports the World Federation of Neurology (WFN) and other neurological associations in accomplishing that mission.

He has been associated with the Foundation for more than a decade and was Vice-President from 2007 until he succeeded Dr. Michael Finkel as President in April.

TARAKAD RAMACHANDRAN, MD, MPH, MBA

Dr. Ramachandran has a strong interest in vascular neurology (stroke medicine) and is highly regarded nationally and internationally as a clinician and educator. He moved to Syracuse, N.Y., USA, in 1976 from the United Kingdom, where he trained in internal medicine. After 2 years of residency and a year of chief residency in neurology at State University of New York's Upstate Medical University, Syracuse, he was a fellow in neuromuscular diseases and electrophysiology at Boston University School of Medicine. He returned to Syracuse in 1980 to pursue his career in neurology at Crouse and University hospitals.

In addition to being a full academic professor in neurology, Dr. Ramachandran also has held positions as clinical professor in neurosurgery, internal medicine, and family medicine and a lecturer for the Center of Bioethics and Humanities at Upstate Medical University.

Dr. Ramachandran chaired Crouse's Operation Stroke Committee from 1996 to 2000. As chief of neurology at Crouse, he was instrumental in creating the hospital's stroke unit, the first in the upstate New York region to be designated with "Gold Plus" performance achievement from the American Stroke Association. He also was active in establishing the stroke unit at Upstate Medical University, from which he retired in 2010. He is presently director of neurosciences at Crouse Hospital and professor emeritus in neurology and psychiatry at Upstate Medical University.

Dr. Ramachandran has published widely and has received many honors and awards. In 2007, the American Academy awarded him the A.B. Baker Teaching Award; and, in 2008, he was the recipient of the AAN's Kenneth M. Viste Jr. Patient Advocate of the Year award for helping establish an imaging center in Pune, India, to provide free computerized tomography scans and free clinics to the poor. He used the clinics as a base for teaching Indian medical students and residents. This year, he received the Leonard Tow Humanism in Medicine Award from the Arnold P. Gold Foundation for outstanding compassion in the delivery of care; respect for patients, their families, and health care colleagues; and clinical excellence.

As a delegate of the World Stroke Foundation, he participated in the inauguration of the Regional Asian Stroke Congress and first Indian Stroke Association Meeting, endorsed by the World Stroke Federation, at Chennai, India, in 2006. Ever since, he has been a visiting faculty at the Indian Stroke Association's annual meetings and has contributed significantly to neurological training and teaching elsewhere in India. Dr. Ramachandran is a fellow of the American Academy of Neurology. He also holds master's degrees in business administration from SUNY Binghamton University and in public health from Upstate and Syracuse universities. ■

World Neurology

World Neurology, an official publication of the World Federation of Neurology, provides reports from the leadership of the WFN, its member societies, neurologists around the globe, and news from the cutting edge of clinical neurology. Content for World Neurology is provided by the World Federation of Neurology and Elsevier Global Medical News.

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PRESIDENT'S COLUMN

Moving Into the Next Phase

VLADIMIR HACHINSKI, MD

The best time to plan change is during stability, which is also the most challenging time to do it. The World Federation of Neurology has grown from strength to strength in its half century of existence, but neurology and the world have been changing even more rapidly, and it takes careful and continual planning for us to keep apace with them.

Our administration began with a planning and priorities retreat in London in July 2010, where we reformulated the WFN mission **to foster quality neurology care and brain health worldwide**. Quality implies standards. One way to set standards is by evaluating what we endorse, so the WFN has formed a Standards and Evaluation Task Force made up of Sarosh Katrak (India) and Charles Warlow (UK), and chaired by Aksel Siva (Turkey), which reviews applications to use the WFN logo for the endorsement of congresses and meetings. Our activities are guided by the answer to four questions:

- What is the value? We favor low-cost, high-impact activities.
- What is the synergy? How can the activity be leveraged within the WFN or with other organizations?
- What is the viability? We cannot afford to disperse our limited resources on one-off projects. We need to know the activity will either be completed with the allocated resources or that another organization or government will carry on with the project.
- What will be the process of evaluation? What gets measured, gets done.

In the first phase of this administration, we have kept the committees small so that members could learn to work with each other and with the mission and guiding questions in mind. We have set our priorities, and for the first time have begun a grant review process and funding of member-initiated projects, with several being cofinanced by other organizations, such as the World Stroke Organization and the International League Against Epilepsy. The Grants Review Committee is chaired by me and includes Murat Emre (Turkey), Sarosh Katrak (India), and Jun Kimura (Japan and USA).

All appointments within the WFN have been made for 2 years (tenures of positions ending on Dec. 31, 2011). Now that priorities are set and a number of projects have been funded, opportunities for new appointments and enlargement of the number of task forces will allow for wider participation by members of the WFN.

The World Congress of Neurology (WCN) in Marrakesh, Morocco, Nov. 12-17, will be a great platform for our members to interact, and by all indications it is going to be a landmark event. Registrations to date are comparable with the period leading up to the 2009 Congress in Bangkok, with a total of more than 1,400. The scientific program is outstanding because of the combined efforts of the numerous WFN committees and their colleagues on the Moroccan local organizing committee, who have involved the entire region it the planning. The king of Morocco, His Majesty Mohammed VI, will be sponsoring a gala dinner. This is the first time that a head of state has done so for a World Congress of Neurology, and we are honored and grateful.

In addition to the Council of Delegates and the meetings of the various committees and task forces, WFN Vice-President Werner Hacke and Donna Bergen, chair of the Applied Research Committee, will convene a special session of the Applied Research Committee and brain specialty, neurology subspecialty, and related organizations to integrate and collaborate the activities of the diverse organizations dealing with the brain. This is to complement the World Brain Alliance (WORLD NEUROLOGY, April 2011, p. 3; June 2001, p. 3). Finally, the updated and enhanced WFN website will be launched at the Marrakesh Congress by Dr. Jerome (Pete) Engel, the web editor and his committee members.

The first phase of our administration has set the stage for an accelerated second phase: *Festina lente* (make haste slowly).

I am looking forward to seeing you in Marrakesh! ■

WCN 2011

Countdown to Marrakesh

The program for the 20th World Congress of Neurology in Marrakesh, Morocco, Nov. 12-17, includes a line-up of scientific and teaching sessions – and a host of social events with a decidedly local flavor.

In keeping with this year's theme of "With Africa, for Africa," the scientific program for the 20th World Congress of Neurology will include several sessions that focus on the practice of neurology on the continent, in addition to presentations on the latest research findings and new therapies.

Beginning on Saturday, Nov. 12, there will be a teaching session on neurological disorders in sub-Saharan Africa. Other topics during the course of the congress include neuroepidemiological issues in Africa, the history of neuroscience in the Maghreb, and neurological care policy in Africa. There will also be three sessions covering dementia, epilepsy, and cognitive impairment in developing countries.

In all, there will be 13 plenary lectures given on an array of neurological topics by leading experts. Among those featured speakers are:

PROF. CHRISTIAN E. ELGER

- **Prof. Christian E. Elger**, who will deliver the Soriano Lecture on Sunday, Nov. 13, titled "Key Questions on Epileptology." Prof. Elger is the director and head of the department of epileptology at the University of Bonn, Germany. He has held research fellow posts at the University of Zürich, Switzerland, and the University of Tennessee, in Knoxville, USA. He has served as president of the German Society of Clinical Neurophysiology and chairman of the German division of the International League Against Epilepsy, where he has been a member of the Committee of European Affairs. Prof. Elger is an associate editor for *Epilepsy & Behavior* and has published numerous articles on experimental and clinical epileptology, and cognitive research.

DR. DAVID ZEE

- **Dr. David Zee**, who will lecture on "Vertigo and Balance" on Tuesday, Nov. 15. Dr. Zee has been a member of the medical community at Johns Hopkins University in Baltimore, Md., USA, for more than 4 decades as a student and faculty member. He has a special interest in vision and eye movements, cerebellar function and motor learning, and vestibular disorders. He has received the Ottorino Rossi Award from the University of Pavia in Italy for his work on eye movements, and the Hallpike-Nylen Medal of the Bárány Society in Sweden. He served as the Inaugural Visiting Professor of Neurological Education at the Mayo Clinic in Rochester, Minn., USA.

PROF. STEPHEN DAVIS

- **Prof. Stephen Davis**, who will lecture on "Translational Stroke Research" on Thursday, Nov. 17. He is the inaugural Professor of Translational Neuroscience at the University of Melbourne, Australia, and is based at the Royal Melbourne Hospital, where he is the director of neurosciences and continuing care, director of neurology and director of the Melbourne Brain Centre at the hospital. Prof. Davis is the immediate past-president of the Australian and New Zealand Association of Neurologists and a past-president of the Stroke Society of Australasia. He is currently on the boards of several associations relating to neurology and stroke and is the recipient of numerous distinguished awards on the translational stroke research.

Social Events

WCN 2011 participants will be treated to especially unique and enchanting social events. On Sunday, Nov. 13, there will be a Moroccan-themed opening ceremony, followed by a welcome reception at the congress venue.

The highlight of the social events program will be a gala dinner on Tuesday, Nov. 15, sponsored by the king of Morocco, His Majesty Mohammed VI. The dinner will be held at the renowned restaurant, Chez Ali, where the five-course feast will be served in an authentic Moroccan setting under caidal tents. During the meal, there will be an unforgettable performance of traditional music and dance by Moroccan performers. Chez Ali is considered to be one of the city's top restaurants in the city.

The Congress at Your Fingertips

- For more information on WCN 2011, go to **www.wcn-neurology.org**.
- To access the interactive scientific program online, go to **www.sessionplan.com/WCN2011**.
- Delegates from Africa and developing countries on other continents are eligible for significant discounts on registration. For more information, go to **www2.kenes.com/wcn/RegAcc/Pages/Reg.htm**. ■

WFN NEW MEMBER – BURKINA FASO

Care, Research, and Education Are Society's Focus

Burkina Faso is a small, landlocked country in West Africa bordering on the Ivory Coast, Mali, Ghana, Togo, Benin, and Niger. Of its total population of 14 million, 52% are female, about 48% are younger than 15 years of age, and 78% live in rural areas. The country is fairly stable politically and as a society, but its gross economic and development data are those of a low-income country. It has three schools of medicine, one of which is private.

Health Issues, Clinical Practices

There are fewer than 1,000 physicians in Burkina Faso, so the country has not yet met the World Health Organization's criteria of 1 physician per 10,000 inhabitants. Its health policy is based on the principles laid out in the Declaration of Alma Ata (WHO, 1978) and the Bamako Initiative (WHO, UNICEF, 1987).

Infectious diseases, mainly in children, are the priority of health policy makers, although HIV/AIDS infection (which affects about 2% of the population, many of whom are adult) presents a significant neurological disease burden. Nontransmissible diseases such as high blood pressure, stroke, diabetes mellitus, and nutritional disorders are increasing and of concern to doctors and policy makers. Health facilities are concentrated in the urban areas of Ouagadougou and Bobo Dioulasso, which are where almost all of the country's 2,000 hospital beds are to be found. The country obtained the first of three CT scanners in 2000, and its first EEG machine in 1992. MRI is not available in Burkina Faso.

Health insurance and third-party payers are uncommon, leading to poor clinical practice and a high incidence of herbal and traditional medicine practices.

State and Practice of Neurology

Clinical neurology care by a trained neurologist dates back to October 1987, when the country's first neurologist joined the internal medicine department of Yalgado Ouédraogo. The first department specifically dedicated to clinical neurology was created at Yalgado Ouédraogo in 2002, and it now has a staff of two neurologists and 10 nurses. There is only one neurosurgeon, who has to tend to the neurosurgical complications of road traffic accidents, brain and spinal cord tumors, and malformations. There are seven psychiatrists and no child neurologists.

BY JEAN KABORE, MD

Dr. Kabore is president of the Burkina Faso Society of Neurology and chair of the neurology department Yalgado Ouédraogo (university teaching hospital) in Ouagadougou, Burkina Faso, where he also practices as a neurologist.

The first local neurological association was formed in February 1992 in response to the growing burden of epilepsy. At that time, more than 500 patients were on file as having epilepsy, prompting a group of psychiatrists, social workers, and nurses to come together to form the Burkina League Against Epilepsy. Studies in rural areas have reported a prevalence of 10.6-16 people with epilepsy per 1,000 of the population. The main etiologies are parasitic and infectious diseases of the nervous system, of which neurocysticercosis accounts for 10%-20% of cases (African J. Neurol. Sci. 1995;14:24-6). We have not been able to find a link between epilepsy and onchocerciasis, even though the prevalence of epilepsy is higher in the Volta River Basin (16 per 1,000) where onchocerciasis occurrence is elevated, compared with other areas of the country (10.6 per 1,000 in the central region; Lancet 1996; 347:836).

But practice of tropical neurology in a low-income country is superseded by many other overwhelming concerns such as stroke and metabolic, infectious, and neurodegenerative disorders. Studies with other countries of western Africa have determined the role of retroviruses (specifically HTLV1) that account for 15.9% in the etiologies of tropical spastic paraplegia (J. Trop. Geograph. Neurol. 1991;1:39-44). Genetic disorders such as hemoglobinopathies (sickle cell disease, in 2%-5% of the population) and thalassemia, are widespread. Neurogenetic disorders such as Huntington's disease (five families described, three with a genetic study accounting for fewer than 3 cases per 100,000; La Revue Neurologique [Paris] 2000;156:1157-58) and genodermatosis (Bourneville's disease and Recklinghausen's disease) have been described. Parkinson's disease and other movement disorders have been noted in patients in early adulthood (age 35-40 years). Alzheimer-related dementia accounts for 19% of all dementia cases, and only 52% of all cases have a known etiology, according to data in an unpublished study by a master's degree student who identified 72 cases of dementias among 15,815 inpatients at Yalgado Ouédraogo during 2007. Cytogenetic and pathological studies are not available.

Child neurology is a hugely unexplored field, with seizure, nutritional disorders, and nervous system infections among the most pressing concerns. To date, poliomyelitis is still a public health concern in Burkina Faso and other West African countries.

The Burkina Society of Neurology

Our society was formed in 2008, and we joined the World Federation of Neurology in 2009. There are seven society members; all are clinical neurologists. Our challenges are evident if one considers how few neurologists there are in the country, the limited opportunities for training, and the lack of funding for promoting better practice. But our goal is always the same: to assist and provide care for individuals who are affected by neurological disease, and to promote research and education in the field.

Our vice-president is Athanase Millogo, MD, a practicing neurologist and chair of the neurology department at Bobo Dioulasso. Christian Napon, MD, is the secretary, and Raphael Kabore is the treasurer. ■

Cardiovascular Disease Deaths Spike in Poor Countries

A global analysis released ahead of last month's United Nations meeting in New York on noncommunicable diseases, revealed that some of the poorest countries in the world have among the highest age-standardized mortality rates of cardiovascular disease (CVD), according to a statement from the World Stroke Organization (WSO).

"It is no longer the case that the majority of deaths are caused by infectious disease," Prof. Bo Norrving, president of the WSO said in the statement. "This data provides the evidence for the necessity of [the] summit; the world needs to invest much more and more quickly in preventing and treating CVD. There is no time to lose."

The organization said that the data in the Global Atlas on Cardiovascular Disease Prevention and Control, a joint publication of the World Health Organization (WHO), the World Heart Federation, and WSO, highlight the increasing discrepancies in the number of cases and deaths of CVD between high- and low-income countries.

The percentage of premature deaths from CVD in low-income countries was reported as more than double that in high-income countries. Other data in the publication demonstrated that efforts driven by government policy and at the individual level to curb CVD risk can substantially reduce the health and socioeconomic burden caused by CVDs.

"Heart disease and stroke, together with other cardiovascular diseases, are often wrongly seen as diseases of affluence, although they affect the poor as well as the rich," said Dr Shanthi Mendis, the WHO's coordinator of CVD, said in the statement. "Although death rates from CVD have been declining in high-income countries over the past 2 decades, they have increased at an astonishingly fast rate in low- and middle-income countries. Now is the time for us to invest in affordable health interventions to ensure that the world's poorest people are not subject to the growing CVD burden in addition to communicable diseases."

'THE WORLD NEEDS TO INVEST MUCH MORE AND MORE QUICKLY IN PREVENTING AND TREATING CVD. THERE IS NO TIME TO LOSE.'

CVD is the biggest cause of deaths worldwide, even though it could be prevented through lifestyle modifications such as reducing tobacco use and alcohol consumption, eating healthily, exercising regularly, and improving primary care. In 2008, there were more than 17 million CVD deaths worldwide, with 82% of those deaths occurring in low- and middle-income countries and 3 million occurring before the age of 60.

Prof. Pekka Puska of the World Heart Federation said that governments could play an important role in to reducing exposure to CVD by introducing policies that ban tobacco, limit the sugar, saturated fat, and salt content of foods, encourage physical activity, and raise taxes on alcohol. He emphasized that such steps to reduce the risk factors for CVD together with improved access to primary health care could save millions of lives.

► Each Oct. 29, the World Stroke Organization (WSO) and its members around the world mark World Stroke Day to promote global awareness of the incidence and consequences of stroke and CVD and advance its campaign to reduce unnecessary deaths from this preventable disease and provide access to care for its victims.

In 2010, the WSO launched the "1 in 6"advocacy campaign – a reference to the fact that currently, one in six people worldwide will have a stroke in their lifetime and every 6 seconds someone will die from a stroke. In addition to promoting awareness of stroke and access to care, the WSO also fosters best clinical practices and facilitates research and teaching in the field. ■

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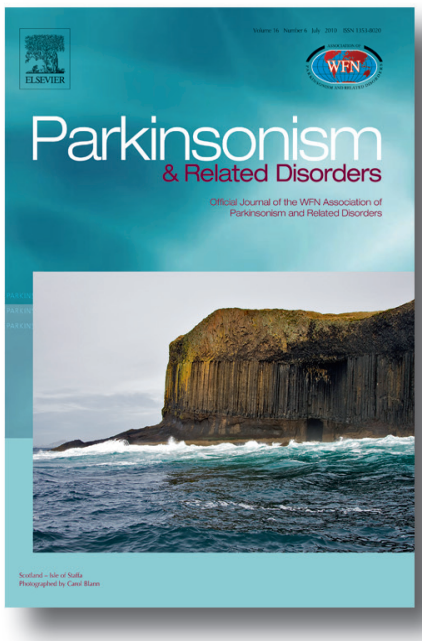

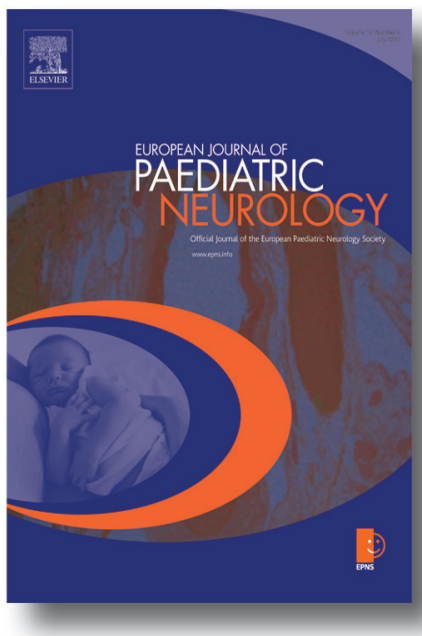

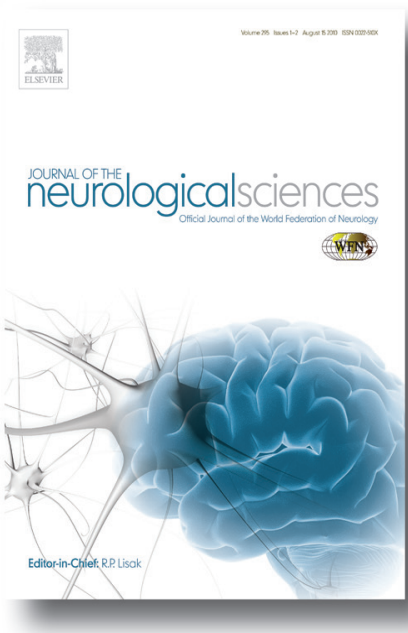

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NEUROLOGY

Gustavo Román

Román Elections • *from page 1*

President of the World Federation of Neurology and his coauthors (Arch. Neurol. 1987;44:21-3). After specializing in Paris, I completed a neurology residency at the University of Vermont in Burlington, USA, under the direction of the late Charles M. Poser, and a fellowship in neuropathology directed by Prof. Daniel Perl.

Investigations in Tropical Neurology

On my return to Columbia, my interests turned to tropical neurology, and I coauthored one of the first books in Latin America on tropical neurology (Toro G, Navarro-Román LI, Román GC. *Tropical Neurology: Neuropathological Aspects of Tropical Medicine*. Colombiana: Bogotá, Colombia, 1983). The year before that, I had met Dr. Bruce Schoenberg, then chief of the neuroepidemiology branch at the National Institutes of Health (NIH) in Bethesda, Md., USA, and Dr. Peter Spencer, a neurotoxicologist at the Albert Einstein College of Medicine in New York, who were in Bogotá to investigate an outbreak of tropical spastic paraparesis (TSP) in Colombia. During the next 2 years, the National Institute of Health of Colombia sponsored an intensive research study on TSP, and Lydia and I worked in the small island of Tumaco on what would become my baptism-of-fire introduction to neuroepidemiology. Under Dr. Schoenberg's masterful direction, we were able to describe the natural history of this geographic focus of TSP (Ann. Neurol. 1985;17:361-5; Neurology 1985;35:1158-70). Soon after that, I joined the neurology faculty at Texas Tech University in Lubbock, USA, and within a short while, I resumed working with Dr. Schoenberg and Dr. Peter Spencer on another outbreak of TSP, this time in the Seychelles Islands. We eventually confirmed the disease's retroviral origin, and the history of the discovery of HTLV-I myelitis has been recently reviewed (Lancet Neurol. 2007;6:104-5).

In 1990, I succeeded Dr. Schoenberg, who had become seriously ill, as chief of neuroepidemiology at the NIH. I continued the research on TSP in the Caribbean and South America and among other topics, organized a workshop that proposed the research criteria for vascular dementia, which are currently used worldwide (Neurology 1993;43:250-60). One of the most challenging research activities at the NIH was when we participated in a study of an epidemic of optic and peripheral neuropathy in Cuba that had affected more than 50,000 people and was probably the largest neurological epidemic of the past century.

Same Principles, Different Diseases

During this time, I was quite active with the WFN research groups on neuroepidemiology and tropical neurology. We conducted numerous courses on neuroepidemiology that helped promote a research network that continues to provide data on the epidemiology of dementia, Alzheimer's and Parkinson's diseases, and vascular dementia in China, Spain, Argentina, and Mexico.

In 2000, I joined the University of Texas Health Science Center at San Antonio, USA, where I established the Alzheimer Disease Memory Clinic, which was invited to join the Texas Alzheimer Research Consortium. I participated in a large study funded by the NIH on prevention of lacunar strokes and cognitive loss with control of hypertension (SPS3).

Last year, I was selected as the Jack S. Blanton Distinguished Endowed Chair and director of the Alzheimer's Disease Clinical and Research Center at The Methodist Neurological Institute in Houston, USA. In this capacity, I continue to apply the principles of epidemiology and the teachings of my mentors in clinical neurology and neuropathology to find a solution to the cruelest neurological epidemic of our time, Alzheimer's disease.

I began serving as Elected Trustee of the WFN in 2009 during the World Congress of Neurology in Thailand and at the request of the President of the WFN, I accepted the task of directing the WFN Latin American initiative. As Elected Trustee, I have participated in all the major administrative decisions of the current board of directors of the WFN. Also, I served as faculty in the teaching course for African neurologists organized in 2010 by the European Federation of Neurological Societies (EFNS) and the University of Cocody, in Abidjan, Ivory Coast, and was instrumental in inviting and welcoming Ivorian neurologists as new members of the WFN. I lectured at the meeting of the Pan American Society of Neuroepidemiology in Punta del Este (Uruguay) and the 3rd Latin American Meeting of the Dementia Group of the WFN in Buenos Aires (Argentina). I was invited to serve as adviser for the scientific program of the forthcoming 20th World Congress of Neurology in Marrakesh, Morocco, and of the 13th Pan American Congress of Neurology (4-8 March, 2012) in La Paz, Bolivia.

Mission Statement

Very early in life I learned that education is critical to overcome the limitations imposed by environment and economic restrictions. I believe that education is also the answer to many of the problems resulting from uncontrolled risk factors in populations such as hypertension, malnutrition, trauma, and violence, among others, that are the preventable causes of many neurological diseases; whereby, public health practice and policy becomes an important tool for neurologists. By the same token, increasing the number and the educational level of neurologists must result in tangible benefits for the countries and their peoples. With the change to a bienniel schedule of the World Congress of Neurology, the duration of service of the Elected Trustees has also been limited to only 2 years. Therefore, I am seeking re-election as Trustee of the WFN in order to bring to full fruition the projects I have already started. ■

John Wokke

Wokke Elections • *from page 1*

introduced me to the fascinating field of specialized light and electron microscopy. Prof. Jennekens and I subsequently collaborated with the late Prof. John Newsom-Davis and Prof. Hans Oosterhuis in research on congenital myasthenic syndromes.

In 1988, I defended my doctoral thesis on human motor end plates, in which I showed that nerves continue to create new end plates during aging and disease. This notion of plasticity of the end plates is very reassuring. I argued that the skeletal muscle satellite cells around human motor end plates may facilitate this regenerating process. The year before I defended my thesis, I was one of the first researchers to describe the CNS manifestations of Lyme disease (Neurology 1987;37:1031-34).

Probing the ALS Puzzle

My colleagues in the department of neurology at Utrecht and I formed a research group, focusing our work on multifocal motor neuropathy (MMN), chronic inflammatory demyelinating polyneuropathy (CIDP), and motor neuron disease and amyotrophic lateral sclerosis (ALS). Initially, we described the natural disease course, neurophysiological characteristics, and effects of the treatments for MMN and CIDP. In 2010, we monitored the response of 88 MMN patients to IV immunoglobulin (IVIG) treatment and reported findings that suggested that early IVIG treatment might postpone axonal degeneration and permanent deficits (Neurology 2010;75:818-25). I have compiled a nationwide database of ALS patients with the present research group leader, Prof. Leonard van den Berg, a leading expert of whole genome analysis of ALS. Our goal is to unravel the genetic and environmental factors that could be risk factors or disease-modifying factors for ALS. We believe that this knowledge could inform the discovery of new treatments. I was very fortunate to collaborate for many years with the eminent stroke neurologist Prof. Jan van Gijn, a former head of the department of neurology at Utrecht and one of the founding members of the European Neurological Society. We focused the department's research on stroke and neuromuscular diseases.

Education, Research, and Care

I chaired the department of neurology from 2001 to 2011. My colleagues and I have always tried to bring in enthusiastic, talented students to work with us in our research. Many of these research students will become neurology residents and clinical researchers. Over the years, I have supervised 24 doctoral students, most of whom are neurologists now. Many continue with research or are involved in neurology education. For me, teaching and research go hand in hand. Young doctors should question existing knowledge and contribute to expanding the knowledge base. If they do not do that, who will? I firmly believe that university departments must try to make a difference and improve the scientific basis for good patient care.

At present, all 36 residents of the department combine neurology training with clinical research into ALS, stroke, or epilepsy in children for their doctoral theses. Five of our residents have been appointed professors at other institutions.

I have long been involved in the European neurological community, and I see my involvement there as a stepping stone to the global community. Connection and collaboration between neurologists and researchers across the world are important for the development of our specialty. Studies of phenotypes, clinical trials, and genetics improve with the contributions from doctors from various countries because the external validity of results will increase. Of course, the best methodology is a prerequisite.

In 1996, I organized the sixth meeting of the European Neurological Society in The Hague. In 2000, Prof. Pamela Shaw, Prof. Nigel Leigh, Prof. Vincent Meininger, and I founded the European ALS Study Group to encourage young scientists to pursue ALS research. The group holds low-key meetings at which junior researchers present their work and senior experts and researchers from some of Europe's leading ALS research centers offer comment and feedback. Such meetings help build mutual trust and foster scientific exchange and the formation of networks. From 2006 to 2009, I chaired the Dutch Society of Neurology. During my tenure as chair, we drew up a new strategy for the specialty that emphasized quality of neurological care, education, scientific developments, and neurological practice. I am currently chairman-elect of the education committee of the Dutch Society of Neurology.

Mission Statement

Throughout my career, I have always stressed the equal importance of education and research. In 1988, I received the young investigator award from the Amsterdam Neurological Society, and in 2001 I received the Winkler award for research on neuropathies and ALS from the Dutch Society of Neurology. The Winkler is awarded every 5 years. In 2010, I received the Vaandragersprijs teaching prize from the society of Dutch neurology residents.

In the next phase of my career, I intend to focus upon improving neurology education and quality of neurological patient care. As a WFN Trustee, I would hope to contribute to help setting international standards for neurological education and to improve exchange between various countries. Second, with the rapid development of research and of special fields of interest in neurology, the specialty as a whole in and between countries should be guarded and improved. Training in good clinical thinking can help to achieve just that. Formulation of international accepted standards, guidelines, and practice parameters is another tool. In both areas, a role for the WFN is evident. ■

SSRIs May Up Kids' Risk of Limb Movements in Sleep

BY SHARON WORCESTER
Elsevier Global Medical News

Children who are treated with selective serotonin reuptake inhibitors have fivefold greater odds of experiencing periodic limb movements of sleep than do those who are not treated with SSRIs, according to findings from a retrospective review of polysomnography data.

Nearly a third (31.7%) of 41 children receiving SSRIs at the time of the study experienced periodic limb movements of sleep, compared with only 7.8% of 982 children not receiving SSRIs (odds ratio, 5.45), Dr. Martina Vendrame of Boston University and her colleagues reported.

Furthermore, the median periodic limb movement index in those receiving SSRIs was significantly higher than the index in those not receiving SSRIs (11.2 vs. 6.5), the investigators said (Pediatr. Neurol. 2011;45:175-7).

Although periodic limb movements of sleep have been reported in adults taking serotonergic antidepressants – with one study showing that 44% of adults receiving fluoxetine experienced the symptoms, and others showing that restless legs syndrome (RLS) is exacerbated in up to 10% of adult patients on SSRIs – the current study is one of few that provide information about periodic limb movements of sleep in children and adolescents.

Study subjects were all children who underwent overnight diagnostic polysomnography between January 2009 and April 2010 at a single center. The studies were conducted for various sleep disturbances such as snoring, pauses in breathing, daytime sleepiness, and gasping or snorting in sleep; none was conducted for reports of RLS or periodic limb movements of sleep.

The patients who received SSRIs included 31 girls and 10 boys who had a median age of 15.4 years. The SSRIs were prescribed for depression and included citalopram or escitalopram in 15 patients, fluoxetine in 14 patients, and sertraline in 12 patients.

"The mechanism by which SSRIs may cause periodic limb movements of sleep is not clear, but serotonin-mediated dopaminergic inhibition may represent the underlying mechanism," the investigators noted.

Although no significant differences in mean periodic limb movements of sleep indices were seen between different SSRIs in this study, it is possible that different doses and timing of administration could result in better control of limb movements, they said, adding that when periodic limb movements of sleep are found, a careful history should be taken to assess whether they are causing sleep disturbance, and also to determine if the child is experiencing RLS.

"If necessary, the use of antidepressants not associated with periodic limb movements of sleep should be considered," they wrote.

Although limited by the use of single-night polysomnography, a small study population, and possibly by referral bias to a tertiary center, the findings suggest that periodic limb movements of sleep may be an important side effect of SSRIs that is frequently overlooked in children.

"Recognition may result in better control of periodic limb movements of sleep and improved quality of life in these patients," Dr. Vendrame and her colleagues concluded, noting that future investigations should include a multicenter, prospective study using multinight polysomnography, investigation of various SSRIs separately, and evaluation of the role of underlying diseases for which subjects are treated with antidepressants in the development of periodic limb movements of sleep. ■

VITALS

Major Finding: Nearly a third (31.7%) of 41 children receiving SSRIs at the time of the study experienced periodic limb movements of sleep, compared with only 7.8% of 982 children not receiving SSRIs (OR, 5.45).

Data Source: A retrospective review of polysomnography data in 1,023 children.

Disclosures: No financial disclosure information was available in the report.

FROM THE WFN HISTORY GROUP

The Evolution of the Reflex Hammer

Some hammers resembled all manner of miniature medieval weaponry: halberds, battle-axes – symbols all of the fight against disease and disorder; magic wands, T-shaped, L-shaped and ball-shaped; tipped or girded with elastic rings, some constructed even as universal tools.

FRANCIS SCHILLER (1967)

COURTESY A MANUAL OF DISEASES OF THE NERVOUS SYSTEM, ©1899

Figure 1. The 'knee jerk' as illustrated in Sir William Gower's *Manual*; note the use of the Vernon percussion hammer.

COURTESY CATHERINE STOREY

Figure 2. Hammers are, from left, the Babinski, Hurst, Queen Square (modern), Berliner, Taylor, and Buck.

The reflex hammer is surely the universal emblem of the neurologist, and the tendon reflex one of the most important components of the neurological examination.

There is documentary proof that the American neurologist S. Weir Mitchell (1840-1921) had described the response of muscles to the tap of a percussion hammer as early as 1859 and that many physicians were aware of the phenomenon, but the first systematic studies of the knee reflex were described in 1875 by the Germans Wilhelm Erb (1840-1921) and Carl Westphal (1833-1921). In two independent publications, Westphal described the "knee phenomenon," and Erb, the "patellar-tendon reflex" (Neurology 1989;39:1542-9).

BY CATHERINE STOREY, OAM, MBBS, MSC, FRACP

Dr. Storey is a neurologist and a clinical associate professor at the Sydney Medical School, University of Sydney, Australia.

Sir William Gowers (1845-1915) would later coin the term "knee jerk." Gowers, in his now famous text, *A Manual of Diseases of the Nervous System (1886-1888)*, stated that this reflex could be elicited using the side of the hand – "Now and then, when very slight, a percussion hammer … or a stethoscope with an India-rubber edge to the earpiece elicits it more readily" (Gowers, WA. *The Diagnosis of Diseases of the Spinal Cord*, 2nd ed., London: J & A Churchill, 1881:19-34.). In an accompanying drawing (Figure 1), the percussion hammer Gowers used can be recognized as that described by another London physician, Dr. Henry Vernon, in *The Lancet* (Feb. 6, 1858, p. 141). Just as Gowers adopted this hammer for the knee jerk, Jean-Martin Charcot (1825-1893) is credited with the use of the Skoda percussion hammer. But those hammers had been designed to percuss the chest.

Chest percussion was originally described in 1761 by the Austrian Leopold Auenbrugger (1722-1809). He was inspired by the practice of tapping wine barrels to determine the level of their contents. The technique however, did not gain immediate popularity. With the emergence of bedside clinical medicine in post-Revolutionary Paris, the art of percussion was revived. A series of refinements to the original finger-tapping method followed. A small disc (a pleximeter) was interposed between the percussing fingers and the bare chest wall and then a small hammer introduced to strike the disc.

In 1841, the German physician Max Wintrich (1812-1882) introduced the first fashionable percussion hammer to Europe. (It is also interesting to note that the use of a hammer may have been a novelty for the physician, but it was well known in veterinary practice. Cowherds had been known to use such a device to determine a resonance caused by cystic lesions, most frequently hydatid disease, in the brains of their animals.)

In Europe, many adaptations of the original Wintrich hammer evolved to elicit tendon reflexes. One such hammer, designed in 1901 by Ernst Troemner (1868-1930) of Hamburg, Germany, became very popular. According to Troemner, his hammer had the added advantage that the smooth handle of the hammer could easily be cleaned and in a pinch used as a tongue blade!

Another German neurologist, Dr. Bernhard Berliner, who considered it "not very elegant to percuss the knee or Achilles tendon with a paperweight, the edge of a large electrode, the foot of a laboratory stand, a table lamp, or similar devices," designed a hatchet-shaped hammer (Figure 2), which he said allowed, in most instances, for the elicitation of an existing Achilles reflex through the patient's boots.

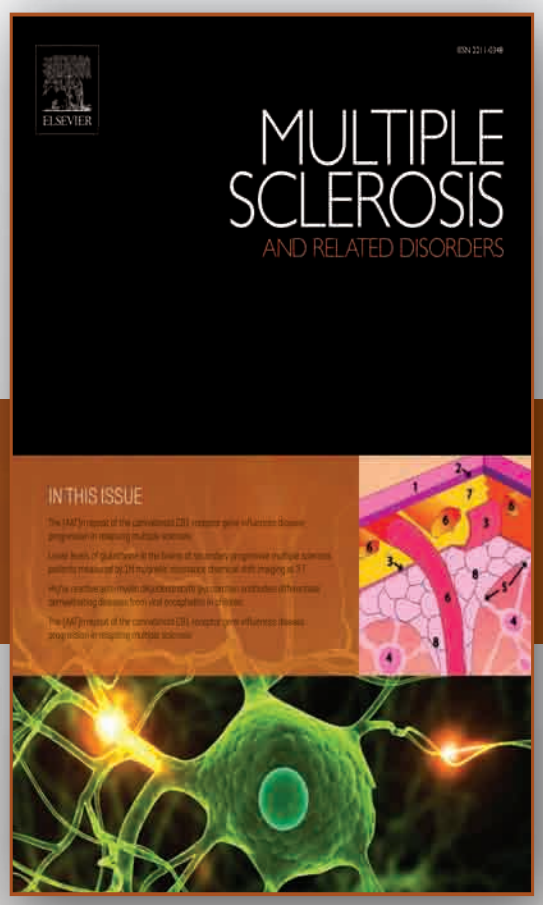
In the United States, Dr. John Madison Taylor (1855-1931) is credited with the design of the first "neurological hammer" (Figure 2). Taylor exhibited his now famous triangular, rubbed-headed hammer in 1888, while he was working as a personal assistant to the prominent neurologist, S. Weir Mitchell (1829-1914). The hammer would later be incorporated into the official logo of the American Academy of Neurology.

The first of the "universal tools" was designed by William Krauss (1863-1909) of New York and exhibited in 1894. The Krauss hammer incorporated a range of adaptations for sensory testing.

During a visit to Europe in 1927, Dr. Henry W Woltman (1889-1964) of the Mayo Clinic in Rochester, Minn., USA, was so impressed with the Troemner hammer that he purchased several of the hammers as presents for his American colleagues. The European-derived Troemner hammer became something of a tradition at the Mayo Clinic.

In London, the Vernon hammer eventually gave way to the now famous "Queen Square" hammer (Figure 2). Macdonald Critchley, according to Schiller, reported that we owe this hammer to a Miss Wintle, head nurse of physiotherapy and radiology at Queen Square – aka, Sister Electrical. According to Critchley, around 1925, she "hit upon the happy device of fitting a ring pessary to a solid brass wheel, and mounting this upon a stick of bamboo. The result was a heavy, springy, and completely painless hammer ... for years, she made these herself … and sold them to postgraduate students at four shillings each ($1 then), 2s. 6d. for resident medical officers" (Med. Hist. 1967;11:75-85). The famous Queen Square hammer is nothing more than a pessary on a bamboo stick! Schiller opines that the hammer became a badge of the ultrasophisticated practitioner of the art. ■

PETER J. KOEHLER, MD, PHD, *is the editor of this column. He is a neurologist in the department of neurology at the Atrium Medical Centre, Heerlen, the Netherlands. Visit his website at www.neurohistory.nl.*



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Aims and Scope

Multiple Sclerosis is an area of ever expanding research and escalating publications.

Multiple Sclerosis and Related Disorders is a wide ranging international journal supported by key researchers from all neuroscience domains that focus on MS and associated disease of the nervous system. The primary aim of this new journal is the rapid publication of high quality original research in the field. Important secondary aims will be timely updates and editorials on important scientific and clinical care advances, controversies in the field, and invited opinion articles from current thought leaders on topical issues. One section of the journal will focus on teaching, written to enhance the practice of community and academic neurologists involved in the care of MS patients. Summaries of key articles written for a lay audience will be provided as an on-line resource.

A team of four chief editors is supported by leading section editors who will commission and appraise original and review articles concerning: clinical neurology, neuroimaging, neuropathology, neuroepidemiology, therapeutics, genetics / transcriptomics, experimental models, neuroimmunology, biomarkers, neuropsychology, neurorehabilitation, measurement scales, teaching, neuroethics and lay communication.

Audience

All branches of neuroscience: clinical neurologists, neurophysiologists, geneticists, psychologists, molecular biologists, MRI and allied imaging specialists, immunologists, major pharmaceutical companies, ethical and legal specialists, MS specialist nurses, drug trial nurses.

Type of articles

- Editorials
- Commentaries
- Original papers
- Clinical Trial papers
- Reviews
- Letter to the Editors
- Case Reports
- Correspondence
- Book reviews
- News
- Teaching Lessons

On-line summary of selected papers of relevance for lay audience

Video presentations of informative cases or webcasts of conference debates could be included as supplementary material. We would encourage correspondence and that would be web based.

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Calendar of International Events

2012

5th European Neurological Conference on Clinical Practices: Neurovascular and Neurodegenerative Diseases
Jan. 27-29
Krakow, Poland
www.enccp.net

8th Annual Update Symposium on Clinical Neurology and Neurophysiology
Feb. 22-23
Tel Aviv, Israel
www.neurophysiology-symposium.com

13th Pan American Congress of Neurology
March 4-8
La Paz, Bolivia
www2.kenes.com/PCN2012

64th Annual Meeting of the American Academy of Neurology
April 21-28
New Orleans, USA
www.aan.com

13th Asian Oceanian Congress of Neurology
June 4-8
Melbourne, Australia
www.aocn2012.com

22th Meeting of the European Neurological Society
June 9-12
Prague, Czech Republic
www.congrex.ch/ens2012

16th Congress of the European Federation of Neurological Societies
Sep. 8-11
Stockholm, Sweden
www.efns.org/efns2012

10th European Congress on Epileptology
Sep. 30-Oct. 4
London, UK
www.epilepsylondon2012.org

8th World Stroke Congress
Oct. 10-13
Brasilia, Brazil
www2.kenes.com/stroke/Pages/Home.aspx

Correction

The affiliation for Maria Stamelou, MD (WORLD NEUROLOGY, June 2011, p. 12), was incorrect. Dr. Stamelou is now at the Sobell Department of Motor Neuroscience and Movement Disorders in the Institute of Neurology at the University College of London, UK, where she is an honorary clinical assistant and research fellow.

Immunoadsorption May Have Relieved Neuro Symptoms of *E. coli*

Researchers posit that the therapy may have removed the toxin and activating immune complexes.

BY JENNIE SMITH
Elsevier Global Medical News

People who developed severe neurological symptoms following *Escherichia coli* infection recovered after being treated with immunoadsorption, a process that removes immunoglobulin G from blood plasma, according to a small observational study in Germany.

Whether they would have recovered anyway is not clear.

'The evidence for the interpretation that immunoadsorption has caused these people to improve is really weak.'

DR. STINGELE

The Shiga toxin–producing *E. coli* O104:H4 outbreak, which began in May 2011 in northern Germany, caused enteritis in nearly 4,000 Germans and hemolytic uremic syndrome (HUS) in more than 800 by the end of July (WORLD NEUROLOGY, August 2011, p. 1).

A number of patients with both enteritis and HUS went on to develop severe neurological complications, including seizures, about a week after their enteritis had subsided. The seriousness and diversity of the neurological symptoms accompanying *E. coli* O104:H4 HUS took many experienced clinicians by surprise, and the symptoms included stimulus-sensitive myoclonus (a type of spasm), psychosis or delirium, severe seizures, and aphasia.

The timing of the onset of neurological symptoms led researchers Dr. Andreas Greinacher and Dr. Sigrun Friesecke of Ernst Moritz Arndt University of Greifswald (Germany) to suspect that an antibody-mediated mechanism was involved.

The 12 patients in Dr. Greinacher and colleagues' study were all infected with *E. coli* O104:H4 and had developed HUS followed by a variety of neurological symptoms (most had more than one).

All but one were female, and all but two had been treated first with therapeutic plasma exchange or complement-blocking antibody (eculizumab) and had not responded. Nine were on mechanical ventilation because of breathing difficulties caused by their neurological symptoms (Lancet 2011 Sept. 5 [doi:10.1016/S0140-6736(11)61253-1]).

Patients were treated with IgG immunoadsorption processing of 12 L of plasma on 2 consecutive days, followed by IgG replacement (0.5 g/kg intravenous IgG) as rescue therapy. Eight patients received at least one additional 12-L session of immunoadsorption therapy, and patients whose symptoms returned following therapy received more. Dr. Greinacher and colleagues assessed neurological changes before and after immunoadsorption, using an established scoring system.

The researchers found that in their cohort, composite neurological symptom scores significantly increased in the 3 days before immunoadsorption to 3.0 and improved to 1.0 in the 3 days after immunoadsorption. Five patients who were intubated were weaned within 5 days of therapy, two within 4 days, and two patients needed continued ventilation for respiratory problems. All patients survived, and 10 had complete neurological and renal function recovery.

The findings led Dr. Greinacher and colleagues to conclude that their experience showed immunoadsorption "can strikingly improve neurological complications in patients with *E. coli* O104:H4-associated hemolytic uremic syndrome," and that this was biologically plausible.

"Onset of neurological symptoms 5-12 days after onset of diarrhea is compatible with a secondary IgG immune response," they wrote, and "selective removal of IgG antibodies by immunoadsorption with immunoglobulin-binding columns resulted in a rapid and robust improvement of neurological symptoms."

COMPOSITE NEUROLOGICAL SYMPTOM SCORES ROSE TO 3.0 BEFORE IMMUNOADSORPTION THERAPY AND IMPROVED TO 1.0 AFTER THERAPY.

The investigators also posited that the immunoadsorption could have "two effects: removal of activating immune complexes and effective removal of the Shiga toxin itself."

Although Dr. Greinacher and colleagues conceded that their study was limited by its observational design, "the reproducible response to immunoadsorption in all patients, and especially the repeated response in case of neurological relapse, suggests that improvements were a true treatment effect and not related to the natural course of the illness," they wrote in their analysis.

However, neurologist Dr. Robert Stingele of the University of Kiel (Germany), who also treated patients with HUS and neurological symptoms, was unconvinced.

Dr. Stingele said in an interview that although his group had treated 52 HUS patients, of whom 27 had developed neurological symptoms during the outbreak, immunoadsorption was not a technique they had considered.

The reason, Dr. Stingele said, "is that we did not think the disease was antibody-mediated. Instead, we went after the toxin."

"It is not really plausible in my opinion that central nervous system disease develops mediated by antibodies [in the case of *E. coli* O104:H4] because it takes a long time for antibodies to be available in high titers," Dr. Stingele said.

"These antibodies, to reach the central nervous system, need to cross the blood-brain barrier," he said.

Moreover, Dr. Stingele said, plasma separation – which his group did attempt, just as Dr. Greinacher and many other treatment teams throughout Germany did during the outbreak – was seen to produce no stepwise improvement, though it should have had at least some effect if the disease were in fact antibody-mediated.

All of the patients in Dr. Stingele's group also fully recovered, including those with the most severe neurological symptoms. "Most were discharged with no neurological symptoms and some with mild symptoms," he said of the patients he saw personally.

"While it's certainly an interesting finding that they recovered after immunoadsorption," Dr. Stingele said of Dr. Greinacher and colleagues' subjects, their recovery was similar to what his own group had seen without it. "The evidence for the interpretation that immunoadsorption has caused these people to improve is really weak."

Even if there were another *E. coli* O104:H4 outbreak, Dr. Stingele said, "I would do the same thing that we did. I would not attempt [immunoadsorption]."

Two of Dr. Greinacher's coauthors, Dr. Stephan B. Felix and Dr. Jan T. Kielstein, disclosed receiving research support and speaker fees from Fresenius Medical Care, which manufacturers the immunoadsorption technology used in the study. None of the other authors disclosed conflicts of interest. Dr. Greinacher and colleagues' study was funded by the University of Greifswald and Hannover (Germany) Medical School. Dr. Stingele disclosed that he had no financial conflicts of interest related to his comment. ■

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Study's Data Need Replication

Narcolepsy • *from page 1*

The findings show that narcolepsy onset in China is strongly seasonal, and suggest that it is not related to H1N1 vaccination. The occurrence of narcolepsy onset was more than threefold greater than expected following the 2009-2010 H1N1 pandemic, but 96% of new narcolepsy patients in 2010 did not report being vaccinated. This is in contrast with reports of narcolepsy in Finland, the United States, France, and Canada following H1N1 vaccination with adjuvanted vaccine (particularly Pandemrix), which had caused alarm in those countries.

Indeed, the findings suggest that winter airway infections – such as those caused by influenza A (including H1N1) and/or *Streptococcus pyogenes* – are triggers for narcolepsy, the investigators wrote, adding that "winter infections would initiate or reactivate an immune response that leads to hypocretin cell loss and narcolepsy in genetically susceptible individuals."

About two-thirds of subjects in prior studies of narcolepsy onset had high titers of ASO (antistreptolysin O) antibody, which is a marker of *S. pyogenes* infection, primarily strep throat, they explained, noting that those findings are complemented by epidemiologic findings showing a 5.4-fold higher risk of narcolepsy in those reporting physician-diagnosed strep throat before age 21 years.

"As *S. pyogenes* is known to be associated with the onset of other autoimmune disease, notably rheumatic heart fever and [Sydenham's] chorea, it was a prime candidate as a potential autoimmune trigger for narcolepsy," they said.

It is difficult to determine, however, whether streptococcus is involved, or is an associated infection, particularly because numerous studies have shown that upper airway infections often involve multiple viral and bacterial coinfections or superinfections, including *S. pyogenes*.

Available data suggest that two factors may be needed for narcolepsy development, including "a specific immune-mimicry component, mediated through the presentation by DQB1*06:02/DQA1*01:02 of a particular autoantigen to a specific [T-cell receptor] idiotype," and "nonspecific factors such as adjuvants, influenza, or strep infections, streptococcus superantigens and other factors," the investigators wrote, noting that studies are currently ongoing to evaluate this.

Although limited by the single-center and retrospective nature of the data, this study nonetheless supports the concept that H1N1 – either alone or with other winter infections – is associated with narcolepsy onset in a temporal manner, which suggests causality, they said.

The new finding of an association with infection – and not vaccination – is important because it suggests that limiting vaccination out of fear of narcolepsy could actually increase overall risk, they added.

In an accompanying commentary, Dr. Stephen L. Hauser and Dr. S. Claiborne Johnston of the University of California, San Francisco, USA, noted there is little evidence to support the claims by the authors of this study that the H1N1 pandemic flu virus accounts for the surge of narcolepsy seen in 2009-2010, other than the fact that the infection had been prevalent the previous winter (Ann. Neurol. 2011 Aug. 22 [doi:10.1002/ana.22590]). However, they thought the data, which they said need to be replicated and confirmed, "add to evidence of a possible association between infection and narcolepsy, and could point to pandemic H1N1 – in addition to streptococcal infection – as a potential environmental culprit."

They also noted that if specific peptides of pandemic H1N1 are shown to interact with narcolepsy-associated genes, an understanding of the triggers of narcolepsy may begin to emerge, potentially leading to new approaches for prevention and treatment.

As for the emerging concerns about adjuvanted vaccine and narcolepsy risk, Dr. Hauser and Dr. Johnston noted that the findings of this study raise the possibility that narcolepsy following infection and vaccination might represent a common immune response to a similar antigenic challenge – a phenomenon seen with ADEM (acute disseminated encephalomyelitis) that can occur following both native infection with measles virus, or after administration of measles vaccine. In the case of ADEM, the risk is far greater with infection than with vaccination.

This study was supported by research grants from the National Science Foundation of China, the Sino-German Center for Research Promotion, the Beijing Municipal Science and Technology commission, and by the Veterans Administration Research Service. One of the authors, reported serving as a consultant and/or providing expert testimony for Jazz Pharmaceuticals, Merck, Mead, and the Federal Trade Commission. Dr. Mignot also has been in discussion with GlaxoSmithKline, the maker of Pandemrix, regarding the funding of contractual research. ■

COMMENTARY

The possibility that narcolepsy could be a rare side effect of H1N1 flu vaccination was first reported by the Swedish and Finnish medical product agencies in August 2010, with a potential link to Pandemrix vaccination containing the adjuvant ASO3 and squalene/alpha-tocopherol.

Last year, within three major world centers of reference for narcolepsy (Montpellier, France; Montreal, Canada; and Stanford [Calif.] University, USA), we reported an unusual increase in abrupt-onset narcolepsy-cataplexy diagnosed within a few months of H1N1 onset. Cases were reported with a clear temporal link between vaccination and disease onset (mean, 8 weeks), with occasionally an unusual clinical presentation with rapid development and severity of both excessive daytime somnolence and cataplexy.

Findings by the World Health Organization indicated a ninefold increased risk of narcolepsy in children and adolescents aged 4-19 years following vaccination with Pandemrix, and findings of the Swedish Medical Products Agency showed that the relative risk of narcolepsy was 6.6 times higher in vaccinated vs. unvaccinated children and adolescents. All of these results contrast with the exciting findings of this study by Dr. Han and colleagues, in which the occurrence of narcolepsy onset was seasonal, significantly influenced by month and calendar year.

In contrast to our results and the Finnish-Swedish studies, this increased incidence cannot be explained by the H1N1 vaccination.

Narcolepsy onset, at least in China, seems highly correlated with seasonal and annual patterns of upper airway infections, including H1N1 influenza, a finding that could, indeed, be explained by the issues regarding the pathophysiology of narcolepsy with cataplexy mentioned by the authors. These issues include a specific immune-mimicry component to an H1N1-related antigen mediated through the presentation by HLA DQB1*06:02, and nonspecific factors, such as adjuvants, influenza, or streptococcus infections.

YVES DAUVILLIERS, MD, PHD, *is with the National Reference Network for Narcolepsy in the department of neurology at Hôpital Gui de Chauliac, Montpellier, France. Dr. Dauvilliers has consulted for UCB Pharma, Cephalon, Bioprojet, and Novartis.*

Many Migraineurs Report Unmet Medical Needs

Almost half of patients with episodic migraine report having at least one unmet medical need, according to findings in a population-based survey of more than 20,000 people. The findings suggest that despite the expanding armamentarium of acute migraine-specific therapies, patient satisfaction with treatment is at best low to moderate for many, Dawn Buse, Ph.D., director of behavioral medicine at the Montefiore Headache Center, New York, said at the annual meeting of the American Headache Society in Washington, DC, USA.

Dr. Buse and her colleagues identified five domains of possible unmet treatment needs:

- Dissatisfaction with current acute treatment.
- Moderate or severe headache-related disability.
- Excessive use of opioids or barbiturates.
- Excessive use of the emergency department or urgent care clinic for headache.
- History of cardiovascualr events that might preclude triptan therapy.

Those with no unmet needs reported a mean of 2 days per month with headache, compared with 3 days per month for the group with one unmet need, and 5 days per month for those with two or more needs. The most common unmet need was headache-related disability of moderate to severe intensity (19%).

–Michele G. Sullivan

To see a video interview with Dr. Buse, scan the QR code or visit www.clinicalneurologynews.com, click on the video icon, and search for "treatment needs unmet in migraine."

Simple Screen for Medication Overuse Headache

Asking two straightforward questions – "Do you take an attack treatment more than 10 days per month?" and "Is this intake on a regular basis?" – can help clinicians quickly screen and identify patients with medication overuse headache.

The traditional approach to diagnosis of medication overuse headache involving the revised International Classification of Headache Disorders (ICHD-II) criteria requires a face-to-face interview that takes considerable clinician time and expertise, Dr. Virginie Dousset told attendees at the International Headache Congress in Berlin, Germany. So she and her colleagues transformed the second edition ICHD-II criteria into four simplified questions for a patient self-administered screening tool. To determine its sensitivity and specificity, they recruited 79 consecutive patients between September 2009 and February 2010 at the Bordeaux (France) Headache Centre at the University of Bordeaux, where Dr. Dousset is director.

Two questions about attack treatment frequency and regular use of medications were combined and had the best sensitivity (95%) and specificity (80%) for identification of medication overuse headache. The question, "Do you have headache on 15 days or more per month?" had 81% sensitivity and 85% specificity. A fourth question was dropped.

–Damian McNamara

To see a video interview with Dr. Dousset, scan the QR code or visit www.clinicalneurologynews.com, click on the video icon, and search for "diagnosing medication overuse headache."

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Array of Genetic Mutations in Hereditary Neuropathies

All patients with pathogenic mutations presented with peripheral neuropathy symptoms before age 1.

BY SHARON WORCESTER
Elsevier Global Medical News

Hereditary neuropathies with onset during infancy are characterized by extensive genetic heterogeneity and clinical variability, according to findings from a study of 77 unrelated patients who presented with symptoms of peripheral neuropathy within their first year of life.

The patients in the study underwent systematic mutation screening by means of direct sequencing of the coding regions of 11 genes, as well as screening of the Charcot-Marie-Tooth type 1A (CMT1A) duplication on chromosome 17p11.2-12. Mutations were identified in 35 (45%) of the 77 patients, Dr. Jonathan Baets of the University of Antwerp (Belgium) and his colleagues reported.

Five patients carried a de novo heterozygous mutation in MPZ, EGR2, PMP22, or MFN2; 4 isolated patients were heterozygous for mutations in NEFL or MPZ, the CMT1A duplication, or a partial PMP22 duplication; 5 patients had mutations in MPZ and the CMT1A duplication transmitted as a dominant trait; 20 patients inherited recessive mutations in GDAP1, MTMR2, SBF2, FGD4, PRX, or SH3TC2 from their unaffected parents; and 1 isolated patient had a novel heterozygous ARG400 Pro mutation in MFN2, the investigators found (Brain 2011 Aug. 11 [doi:10.1093/brain/awr184]).

"Although the overall mutation frequency was high, the genetic heterogeneity is extensive resulting in a diagnostic yield per gene that rarely exceeds more than a few percent of the total cohort," the investigators noted. Recessive mutations were slightly more prevalent in the cohort than were dominant mutations (20 patients vs. 15 patients).

"Other still unknown mutations must exist in addition to yet unreported phenotypic variants associated with known or unknown disease-associated genes," the investigators wrote.

The CMT1A duplication and mutations in MPZ, PMP22, PRX, and SH3TC2 were most common, accounting for 69% of the identified pathogenic variations, they said.

As for clinical presentation, "all patients with pathogenic mutations presented with symptoms suggestive of peripheral neuropathy within the first year of life," they noted.

Three Phenotypic Subgroups

The presenting symptoms were variable, but the investigators identified three phenotypic subgroups that correspond to selected subsets of the genes screened in the study.

The first phenotypic subgroup comprises "genuinely congenital onset phenotypes presenting soon after birth with symptoms such as hypotonia and breathing difficulties." This group typically had de novo mutations in MPZ, EGR2, and PMP22.

"In addition we identified a heterozygous NEFL mutation that was previously reported to cause severe early onset phenotypes. More surprisingly, we detected a previously unreported partial duplication of exon 4 of PMP22 in an isolated patient presenting with a congenital onset phenotype," Dr. Baets and his colleagues reported.

The investigators also noted that the PMP22 exonic duplication "may well be pathogenic through such mechanisms as exon shuffling or insertional translocation."

The second phenotypic subgroup includes patients with early and progressive delay in motor development in the first year of life, and often occurs in combination with early foot deformities after an otherwise normal neonatal period.

"Recessive mutations in FGD4, PRX, MTMR2, SBF2, and GDAP1 are strongly represented in this subgroup. A few patients with dominant mutations in MPZ and MFN2 broaden the spectrum," according to the investigators.

The third subgroup overlaps extensively with the second, and includes patients with a CMT1A duplication and early – and usually congenital – foot deformities. This group typically has normal early motor development with progressive gait difficulty later in childhood.

"These patients represent the far end of the severity spectrum of classical CMT1A. This finding underscores the important of ruling out the CMT1A duplication in any patient with a demyelinating neuropathy, even in very young children," the investigators wrote.

Thorough electrophysiological testing remains the cornerstone of the diagnosis in the context of hereditary neuropathies, the investigators said.

Nerve biopsies are invasive and generally are best avoided when a diagnosis can be established using other methods, they said, but in this study, 19 of 35 patients with mutations underwent neuropathological examination of a sural nerve or skin biopsy, suggesting that such procedures may still be important in the diagnosis of hereditary neuropathies in young children.

Diagnosis Remains Challenging

The authors drew the following general conclusions for genetic testing from the study findings:

- In patients with a congenital disease onset, mutations in dominant genes are more likely to be the cause; mutations in recessive genes are more probable in those with progressive delay in motor development in the first year of life – especially if parents are consanguineous.
- Axonal subtypes are probably restricted to a smaller subset of genes that may be tested preferentially.
- Other findings, such as myelin outfoldings on nerve pathology, may help prioritize molecular testing.
- Similarly, severe and early scoliosis, although suggestive of SH3TC2 mutations, may also be seen in patients who have mutations in other genes, and can be considered a feature that may be found in many types of severe and progressive neuropathy of early childhood.

"In conclusion, reaching a correct genetic diagnosis in children with severe early onset hereditary motor and sensory neuropathy remains a major challenge with conventional screening techniques.

"A future solution for this diagnostic conundrum may lie in the more systematic diagnostic application of recently developed technologies for massive parallel sequencing," the authors wrote. ■

VITALS

Major Finding: Screening of 11 genes identified mutations in 35 (45%) of 77 patients. Five patients carried a de novo heterozygous mutation in MPZ, EGR2, PMP22, or MFN2; 4 isolated patients were heterozygous for mutations in NEFL or MPZ, the CMT1A duplication, or a partial PMP22 duplication; 5 patients had mutations in MPZ and the CMT1A duplication transmitted as a dominant trait; 20 patients inherited recessive mutations in GDAP1, MTMR2, SBF2, FGD4, PRX, or SH3TC2 from their unaffected parents; and 1 isolated patient had a novel heterozygous ARG400 Pro mutation in MFN2.

Data Source: Systematic mutation screening in a cohort of 77 unrelated patients presenting with peripheral neuropathy in the first year of life.

Disclosures: The authors reported no relevant conflicts of interest or disclosures. This study was funded by the University of Antwerp (Belgium), the Fund for Scientific Research, the Medical Foundation Queen Elisabeth, Association Belge Contre les Maladies Neuromusculaires, Interuniversity Attraction Poles P6/43 programme of the Belgian Federal Science Policy Office, "Methusalem excellence grant" of the Flemish government, the Austrian Science Fund, PhD fellowships of the FWO-Flanders, and Bogazici University Research Fund.

COMMENTARY

In this impressive and well-constructed study, the identification of common genes among affected infants, predominantly from European and Middle Eastern regions, should enable more-targeted genetic screens for infants with peripheral neuropathies.

Supporting previous reports, a proportion of the infants had CMT1A. This condition, reported to be responsible for 70% of adults with CMT, clearly has clinical heterogeneity with the capacity to manifest in all age groups.

The screen for the CMT1A mutation is the most widely available, and should be performed prior to proceeding to other, more-complex point mutation analyses in infants and children presenting with demyelinating disease.

One comment in the article relating to SMARD1 (spinal muscular atrophy with respiratory distress type 1), which is caused by mutations in IGHMBP2), could be viewed as controversial, as it implies that this disorder is not a peripheral neuropathy.

But such is not the case, because published data support an axonal phenotype of this disorder. Patients are reported with the IGHMBP2 mutation and also clinical, neurophysiological, and sural nerve–biopsy evidence of a very severe axonal peripheral neuropathy. Exclusion of this group may explain, in part, the small proportion of infants with axonal disease.

The study provides useful information about clinical markers, which were found more consistently with certain mutations, and which were associated with early or late manifestations in infancy. For practitioners who are working in centers that have limited access to genetic screens, where diagnostic closure for children with peripheral neuropathies can be restricted, such markers are of particular value.

Affected children in my center are assessed by their clinical phenotype, neurophysiological findings, and in some cases, their histopathological data. In most of sub-Saharan Africa, little beyond clinical assessment can be undertaken.

The relevance of genetic testing, beyond gaining a definitive diagnosis, is that it will hopefully lead to better management of the patient. Identifying genetic mutations leads to insight into the pathological process and, from this, the possibility that an effective therapeutic intervention might arise.

JO M. WILMSHURST, MBBS, *is head of pediatric neurology and neurophysiology at Red Cross Children's Hospital, University of Cape Town (South Africa). She reported no relevant disclosures.*

FROM THE JOURNAL OF THE NEUROLOGICAL SCIENCES

Corticosteroids May Induce Arrhythmias in MS Patients

BY MICHELE G. SULLIVAN
Elsevier Global Medical News

Cardiac arrhythmias and conduction abnormalities are not uncommon in multiple sclerosis (MS) patients who undergo high-dose methylprednisolone infusions for an acute disease exacerbation.

Smokers and those with higher body mass indices and sphincter control problems were most likely to develop the problems. But all the disturbances were short lived and none required interventions, Dr. Ali Vasheghani-Farahani and his colleagues reported in a study of 52 patients.

Nevertheless, the high incidence of cardiac arrhythmias during and after methylprednisolone infusion warrants close observation of patients after the treatment. The high-risk groups "benefit from cardiac Holter monitoring 12 hours after the steroid pulse therapy to prevent life-threatening adverse events and identification of possible cardiac complications," the authors wrote (J. Neurol. Sci. 2011;309:75-78).

Dr. Vasheghani-Farahani of the Tehran (Iran) University of Medical Sciences and his colleagues examined adverse cardiac events in the patients who received high-dose methylprednisolone pulse therapy for acute disease exacerbation at a mean age of 35 years. Most (69%) of the patients had relapsing-remitting MS, followed by secondary (21%) and primary (10%) progressive disease. They had had MS for a median of 5.5 years. All received 1 g of intravenous methylprednisolone diluted in 500 mL of 5% dextrose, infused over 2 hours during a 3- to 5-day period. Patients underwent Holter monitoring 4 hours before the infusion, during the treatment, and for 18 hours afterward.

The most commonly observed problem was sinus tachycardia, which occurred in 56% before the infusion, 65% during the treatment, and 84% afterward, all of which were significant increases over the baseline. Sinus bradycardia and atrial tachycardia also increased significantly with treatment. Bradycardia was present in 4% before the infusion, 9% during it, and 42% afterward. Atrial tachycardia occurred in 5% of patients before treatment and 5% during treatment, but increased significantly to 13% after treatment.

Three patients experienced atrial fibrillation after treatment. The first was a 62-year-old man with a body mass index of 34 kg/m^2 and bladder and bowel dysfunction. The other two patients had normal BMIs, but both had autonomic bladder and bowel dysfunction.

Some patients also experienced conduction abnormalities, including 10% with sinus arrest or sinus exit block. There were statistically significant increases of premature atrial contraction and premature ventricular contraction both during and after steroid infusions, the authors wrote. "Sinus arrhythmia was present in 10% of the recordings before steroid infusion, which increased to 30% after pulse therapy. All of these types of cardiac arrhythmias were seen in the first 12 hours after pulse therapy."

Ventricular tachycardia, sinus arrest, sinus exit block, atrial fibrillation, and sinus bradycardia were significantly associated with smoking; sinus arrest, sinus exit block, and atrial fibrillation were significantly associated with a BMI of 25 or higher.

Patients with sphincter disturbance were more likely to experience sinus bradycardia and atrial fibrillation. Bowel dysfunction was significantly associated with sinus bradycardia, sinus tachycardia, atrial fibrillation, and premature atrial contractions.

"Corticosteroids, by their mineralocorticoid activity, result in the retention of sodium and intracellular fluids, causing high blood pressure and congestive heart failure," and increasing the risk for atrial fibrillation. No financial disclosure information was available in the report. ■

COMMENTARY

When I was a junior attending neurologist, I had a multiple sclerosis (MS) patient who was having a relapse. I admitted her to hospital to treat her with intravenous methylprednisolone (IVMP). I had no special concerns about this, since I had treated many MS patients with IVMP with no adverse events at all or only some minor euphoria, or mild dyspepsia. Thus, I was quite unprepared for the nurse's call later that day, when she told me that the patient was bradycardic, diaphoretic, and somewhat nauseated. This sounded like a medication side effect but I had given her no such drugs. A consultant cardiologist suggested that the IVMP had a vagotonic effect. She did well, though in a monitored setting. Subsequent courses of IVMP consistently reproduced the bradycardia. Eventually, she required a pacemaker, when the bradycardia occurred even off steroids. I recall her very clearly because of the unique prominence of her symptoms, which included not only arrhythmia, but also other autonomic findings.

The paper by Vasheghani-Farahani et al. suggests that my impression of the rarity of arrhythmias during IVMP is incorrect and that if we were to monitor our patients closely, we would see this much more often. The rarity of symptomatic episodes suggests that these arrhythmias are generally benign and self-limited. However, patients with preexisting cardiac arrhythmias probably should be observed more closely when getting IVMP.

These observations suggest the important question of why arrhythmias occur. Is it an inherent pharmacological effect of the steroid? Is it due to an unmasking of the effects of demyelination of the autonomic tracts in the spinal cord? The high prevalence of autonomic abnormalities especially of bladder and bowel function are compatible with the latter. The authors' suggestion of the effect of sodium and fluid balance abnormalities are probably compatible with this.

It would be interesting to make the same observations in other groups of patients who are treated with high-dose IVMP for diseases that are not known to involve the autonomic nervous system. Potential groups may include cancer and transplant patients. The results will teach us much about the effects various diseases and medications have on autonomic function.

What happened to my patient? Over the years, she developed several autonomic relapses, including diaphoresis, nausea, and orthostatic hypotension. Ironically these responded partially to IVMP. In her, it is most likely that the MS caused the autonomic abnormalities, beginning with bradycardia, and the IVMP unmasked it.

ALEX TSELIS, MD, PHD, *is associate professor of neurology at Wayne State University in Detroit, USA, and book review editor for the Journal of the Neurological Sciences.*

BOOK REVIEW

Bioterrorism Threat Raises Ethics of Animal Research

Uncaged
By Paul McKellips
Vantage Press, 2011

BY JASPER R. DAUBE, MD

Dr. Daube is professor of neurology at the Mayo Clinic in Rochester, Minn., USA.

This remarkable book tells an important story from a different perspective. Physicians are well aware of the importance of animal research for the steady improvements in medical care, but members of the public are not. Two recent books, one by P. Michael Conn and James V. Parker titled *The Animal Research War*, and another by Adrian R. Morrison, *An Odyssey With Animals*, detail attempts by "animal rightists" to stop animal research, but neither book has attracted public interest in the issue. In *Uncaged*, Paul McKellips presents the same issues in a riveting thriller that will likely have broader appeal.

McKellips is executive vice president for the Washington, D.C. (USA)–based Foundation for Biomedical Research and an accomplished film and television producer. In this, his first novel, he presents the horror of animal rightists' goals and the serious damage and risk to others that accompany their efforts.

A military doctor, Commander "Camp" Campbell, and Lieutenant Colonel Leslie Raines, a medical scientist and expert in infectious diseases, combine their skills to subdue the disastrous results of a presidential ban on animal testing. The ban, which has been instigated by an animal rightist group, halts all medical research in the country just as a terrorist group unleashes a bubonic plague by releasing infested rats into the United States from ships docking at American ports. The book is a fast-moving thriller in which the two heroes overcome innumerable obstacles in identifying and overcoming the bioterrorism threat to the human race and grapple with ethical issues that arise with animal research.

While the book is a work of fiction, it is based on the death of 40 al-Qaeda insurgents in North Africa who had been working with the plague, possibly to use it as a weapon. The book is dedicated to the "biomedical researchers, scientists, and physicians who work in universities, medical schools, and veterinary schools as well as pharmaceutical companies, government agencies, and the military who are fighting for our health." ■

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