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WORLD NEUROLOGY

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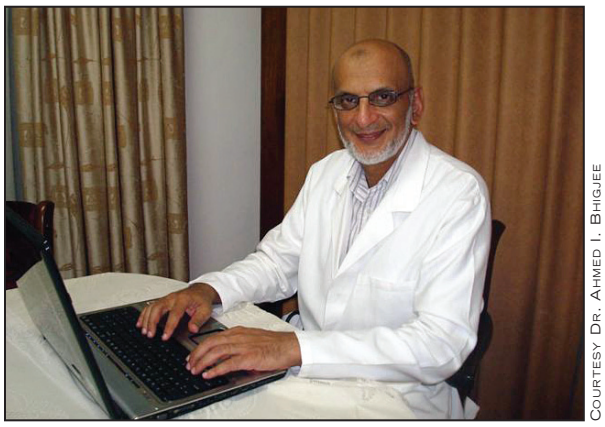
South Africa Battles HIV-Related Disease

BY AHMED I. BHIGJEE, M.D.

South Africa is made up of nine provinces, one of which is KwaZulu-Natal (KZN). As of July 2010, Statistics South Africa has put the estimated population of the country at 49.9 million, of which 10.6 million reside in KZN. The 30-bed neurology unit at the Inkosi Albert Luthuli Central Hospital (IALCH) in Mayville, KZN, and a smaller 12-bed unit at Grey's Hospital in Pietermaritzburg, about 90 km away, are the only neurological facilities in the public sector serving KZN and the northern part of the Eastern Cape, a neighboring province to the south of KZN with a population of 6.7 million people. Only about 20% of the population can afford private health insurance, which means that most patients have to be managed in public sector facilities.

Against the above scenario, one should also note that South Africa probably has the highest infection rate of the human immunodeficiency virus (HIV) in the world. About 5.7 million individuals of the total population (11.4%) are infected.[1] Until recently, the management of this epidemic was bedeviled by the inadequate roll-out of antiretroviral drugs (ARVs). Some of the reasons for the tardy response by the state included the prevailing denialist attitudes about HIV/AIDS, the lack of funding, inadequate staffing, poor infrastructure, and a lack of commitment to addressing the crisis. As a result, most patients who were dependent on the state for care were ARV naive. In turn, many patients presented with advanced disease.

At IALCH, as with other internal medicine units in South Africa's public sector, 50%-60% of the neurological inpatient workload in the state hospitals is HIV related. The range of neurological manifestation of HIV-related disease at IALCH is similar to that in the rest of the country. The following is a discussion of some of the more common or serious neurological complications seen at our hospital.[2]



COURTESY DR. AHMED I. BHIGJEE

Dr. Ahmed I. Bhigjee says HIV accounts for about 55% of neurological workload in South African hospitals.

Neurotuberculosis

The HIV epidemic has made the tuberculosis (TB) problem catastrophic. In 2007, there were about 315,000 cases of new or recurrent TB in South Africa.[3] There has been a corresponding increase in extrapulmonary tuberculosis (EPTB).

▶ **Tuberculous meningitis (TBM)** is the most serious of the EPTB conditions. In HIV-positive patients, it presents in a manner similar to that in HIV-negative patients – fever, headaches, and a change in mental state are common but not invariable. Tuberculous lymphadenopathy is more common in HIV-positive patients, who also suffer complications such as strokes and hydrocephalus. However, HIV-positive patients requiring ventriculoperitoneal shunting have poorer outcomes. No patient with Medical Research Council grade 3 or 4 has survived shunting.[4]

The common difficulty of confirming a diagnosis of TBM in the HIV-negative setting is compounded when there is HIV coinfection. Cerebrospinal fluid (CSF) smears (about 0% positive) and cultures (about 20% positive) have low sensitivity in Southern Africa,[5,6]

See **South Africa** • *page 12*

INSIDE

Premortem Transferrin Level May Flag Creutzfeldt-Jakob

BY MATTHEW STENGER
Elsevier Global Medical News

Low CSF total transferrin level is a reliable premortem marker for sporadic Creutzfeldt-Jakob disease, according to a study by researchers at Case Western Reserve University in Cleveland, Ohio, USA.

Dr. Ajay Singh and her colleagues also reported that performance of diagnostic testing was improved when measurement of total transferrin (T-TF) was combined with measurement of the established sporadic Creutzfeldt-Jakob disease (sCJD) biomarker, total-tau (T-tau).

Sporadic Creutzfeldt-Jakob disease (sCJD) is a rare, fatal prion disorder that typically goes undetected until biopsy or autopsy. This form of CJD occurs in patients in the absence of any known risk factors. It is the most common of the three types of CJD, the others being hereditary and acquired.

In the current study, the researchers obtained human premortem CSF autopsy-confirmed samples from 99 sCJD-positive cases and 75 sCJD-negative cases collected about 10 days to 36 months before death. Following the observation that brain iron dyshomeostasis is accompanied by increased TF in sCJD cases, they measured levels of T-TF and TF isoforms (TF-1 and TF-beta-2) in CSF from the two groups.

Compared with CJD-negative cases, CJD-positive cases had lower median CSF T-TF and higher median T-tau values. T-TF and both TF isoforms were more sensitive differentiators of CJD-positive vs. CJD-negative cases than was T-tau. T-tau showed a significant correlation with duration of sampling prior to death in CJD-positive but not CJD-negative cases, whereas no correlations were observed for the TF markers in either group.

This indicates that "T-tau changes as sCJD progresses,

See **Creutzfeldt-Jakob** • *page 4*

EDITOR IN CHIEF'S COLUMN

The Future of Books

BY MARK HALLETT, M.D.

This issue of World Neurology features three book reviews, two on practical matters of peripheral neuropathies and one on neurological history. Do books matter these days? Does anyone still read them? Should anyone read them? There is plenty of material available in journals, there are lots of review articles, and the Internet is overflowing with information. There are really two issues here; one is the intellectual content of the book, and the other is the format.

As to the content, books have significant value for different types of readers. The value comes from the fact that they can harbor an extended overview of a field as a single entity. It is difficult to get an easily accessible overview by looking at a series of articles, even review articles. A book can be a valuable source for someone learning about a new area because the information often is organized for ease of learning – start with the basics in the front of the book and gradually build up to the more complex details toward the end. This is the textbook. Books can also be useful for more advanced readers who want a systematic approach to a complex topic, perhaps to present a review or organize information into a coherent framework. In addition, books can be helpful just to have on the shelf as a reference. There are many details one needs to remember in medicine, and once you are familiar with a book, you can find what you need quickly.

Let's consider the three books that are reviewed on page 16 as examples. *Companion to Peripheral Neuropathy: Illustrated Cases and New Developments,* by Dr. Peter James Dyck and his coauthors, would be helpful to the generalist or neuromuscular specialist who wants to learn by reviewing cases and to acquire knowledge about how to use modern methods such as MRI. John D. Stewart's *Focal Peripheral Neuropathies* can be read cover to cover, but it will have a long shelf life as a source for quickly checking up on those critical, but easily forgotten details. Justin A. Zivin and John Galbraith Simmons' *tPA for Stroke: The Story of a Controversial Drug* is a modern history of the new therapy, detailing its development. It is at once educational and entertaining. These are all valuable as books.

But what about the format? Some readers must hold the printed book in hand; easy to read after many years of use, and easy to navigate, it allows the reader to shift rapidly from one part of the book to another. Others, mainly younger readers, are happy with electronic media such as the Kindle and iPad. Once a reader is used to these reading devices, they are easy to use, and in addition, they can store many books in a single package about the size of a book. Why do you need a shelf if you have an iPad? Books can also be available online, which blurs the distinction between the "book" and the multiplicity of smaller, generally disconnected items that can be found by searching Google and PubMed. In fact, many books now come with a parallel online version – buy the book and you get to access the same content online. To some extent, this may signal a transition to the future for many books, some of which will be e-only. This may not be bad.

I already think that the printed journal will be gone soon. The important thing is to have the connected intellectual content. The format has to go with the flow. ■

WCN 2011

Team Up for Marrakesh

Education and entertainment will again share a platform at this year's World Congress of Neurology in Marrakesh, Morocco, when participants "exercise their brains" in the Tournament of the Minds.

The popular Tournament of the Minds offers a unique opportunity for competing national teams to interact with their colleagues from other countries and test their clinical prowess and intellectual tenacity. This is the fourth time the World Federation of Neurology has held the tournament at one of its congresses.

"I am thrilled that the Tournament of the Minds will be included in WCN 2011," said Prof. El Mostafa El Alaoui Faris, president of WCN 2011, which will take place Nov. 12-17. "Based on previous tournaments, we know that this dynamic and enjoyable activity enriches the congress for all participants – both professionally and socially."

WFN member societies are invited to enter a team of four neurologists in the tournament. The teams will face each other in a knockout competition, during which they will be asked questions on a range of neurological topics based on clinical cases from around the world. The questions will focus on visual material, videos, and stills, with a minimum of text. The winning team will receive a prize.

All of the teams will participate in a qualifying round. The eight teams that achieve the highest scores will advance to a semifinal round and compete in two groups of four teams, with the winners of each group advancing to the final.

In general, there will be one team per country, but for countries where there are a limited number of neurologists, a team may consist of nationals from more than one country. Congress organizers hope that the tournament will attract competitors from all of the participating countries.

Those who are interested in participating in the tournament should contact the president of the local member society who is responsible for coordinating the national teams.

For more details about the tournament and WCN 2011, visit the WCN Web site at www.wcn-neurology.com. ■

World Neurology

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PRESIDENT'S COLUMN

Brain Health Must Be Part of a World Agenda

BY VLADIMIR HACHINSKI, M.D.

The new administration is a year old, and it is time to take stock. When we began our tenure, we were mindful of striking a balance between continuity and change, on the premise that continuity without questioning presented a risk for obsolescence and that the best time to plan for change was during a time of stability.

One word has guided our thinking throughout the year: **synergy**. Working with others, be they individuals or organizations. That will continue. The World Federation of Neurology (WFN) already has excellent relationships with major institutions such as the European Federation of Neurological Societies, the International Brain Research Organization (IBRO), and the World Health Organization. The Secretary-Treasurer General, Dr. Raad Shakir, for example, chairs the WHO's Topic Advisory Group for Neurology, which is advising on the revision of the International Classification of Diseases in our specialty.

A connection we value especially highly is with the American Academy of Neurology, the largest of our member societies. During the AAN's annual meeting in Toronto last April, a number of WFN Delegates and Committee Chairs, together with the Chairs of the Initiatives and Task Forces, were able to convene with the Federation's Trustees and each other. It is thanks to the Academy's generous and ongoing support in the form of donations of copies of their Continuum journal that we are able to run our extremely successful CME program in developing countries.

The change I referred to at the outset of this column was much in evidence after the Strategic Planning and Priority Setting Retreat in London last June, when the WFN leaders got to know each other and learn about their respective priorities. We began that meeting by exploring what makes the WFN unique: namely, that we are the voice of neurology worldwide. We agreed on a reformulation of the WFN's mission: "**To foster quality neurology and brain health worldwide.**" We addressed many other topics during the 3-day gathering, from regional initiatives to membership dues, and from the Federation's voting system to upgrading its Web site.

Our Annual General Meeting of the Council of Delegates in Geneva in September, during the 14th Congress of the European Federation of Neurological Societies (EFNS), was memorable because it illustrated the extent to which the Federation serves as a platform of unity for the global neurological community. China was absent, but gave its proxy to Taiwan, and the Delegate from Israel moved the acceptance of the Palestinian Neurological Society's application for WFN membership. Neurological societies from Yemen and Ivory Coast became new members of the Federation, which now comprises 113 member societies representing most of the world's neurologists – and through them, the hundreds of millions of current and future neurological patients. Dr. Donna Bergen and Dr. Stephen Sergay, both of the United States, were appointed as Co-opted Trustees to serve with the three Elected Trustees.

Dr. Shakir presented the financial report for 2010. The Federation's operating costs are modest and last year's World Congress in Bangkok fared exceptionally well financially. Nevertheless, we shall be facing increasing costs in our planned investment in the Web site upgrade and our numerous projects. It underlines the importance of seeking partners and fundraising to support these initiatives wherever possible.

Dr. Robert Lisak has done an outstanding job as Editor of the Journal of the Neurological Sciences. During his unprecedented three-term tenure, the Journal's impact factor has increased steadily, its quality has improved, and its profitability has grown. He has agreed to continue in the post until a successor has been appointed (see p. 14).

This year has brought new challenges and opportunities. In September, the United Nations will hold its first-ever Summit on Non-Communicable Diseases, wherein most neurological disorders fall, in New York. Last month, the WFN convened a meeting in Geneva of leaders of international organizations: European Brain Council, IBRO, International Child Neurology Association (see p. 11), World Federation of Neurosurgical Societies, World Federation NeuroRehabilitation, and the World Psychiatric Association. A representative from the World Heart Federation will also be attending. We will all meet with representatives of the WHO. The WFN is doing everything possible to ensure that the brain becomes part of a world agenda. ■

SECRETARY-TREASURER GENERAL'S ANNUAL REPORT FOR 2010

Fiscal Success, Sound Investments Pave the Way for Future Growth

BY RAAD SHAKIR, M.D.

There can be no argument about the World Federation of Neurology's financial highlight of 2010. During October, we finally received our share of the proceeds from the 19th World Congress of Neurology on Bangkok in 2009. Various estimates had been made about the amount we might receive, some of which we scarcely dared hope might be possible. In the end, the sum of £600,206.59 was deposited into the WFN account, exceeding all expectations.

May I record in this column the sincere congratulations of all WFN Officers, Trustees, and members for the excellent way in which the Neurological Society of Thailand, aided by the organizing team from Congrex, achieved such a wonderful and memorable event that was not only a huge scientific and social success, but a highly profitable one as well.

We are now embarking on a period of planned expenditure on certain projects while remaining mindful of the need to safeguard the Federation's future financial health. As President Vladimir Hachinski has made plain in his columns, it is vital that we focus firmly on "modest investment, high-yield activities." We must look for added value at low cost and routine post hoc evaluation of funded activities will inform us on their impact. The WFN cannot assume the role of an ad hoc funding agency: There are more worthy projects than we could possibly afford to support. Nevertheless, the Federation is doing well financially with assets of more than £2.6m and this healthy financial status will allow us to seek partners for some of our new initiatives, raise funds for other initiatives, and invest properly in key activities such as our Web site, which is our face to the world. We are continually examining the roles of our committees and addressing their needs because it is crucial that they receive our support. In addition, the WFN is expanding and diversifying; keeping up with the rapid change is challenging, and all of the Trustees are involved in major decisions regarding the support the Federation provides to various projects worldwide.

It was with the long-term interests of the WFN in mind, however, that I invited our independent financial adviser, Mr. Nick Millar of Ashburn Wealth Management Ltd., Darlington, England, to address the Trustees and the Finance Committee at their meetings during the European Federation of Neurological Societies congress in Geneva last September. He gave invaluable guidance and reminded the Trustees of their fiscal duties and responsibilities under charitable law. With his expert guidance, the Trustees have decided to commit £1,000,000 to a portfolio of investment funds, comprising £600,000 in medium-term investments (4-10 years) and £400,000 in long-term investments (more than 10 years). If, as expected, the next two World Congresses - this year in Marrakesh and Vienna in 2013 - are the all-around successes that previous congresses have been, the Federation could go from strength to strength. ■

It's Time to Pay Those Dues

A friendly reminder that the World Federation of Neurology's 2011 annual fees for your member society are now due.

The subscription is unchanged at £3.00 sterling per member.

It is very important the WFN maintains an up-to-date list of all our members. If there are *any changes to your officers or members, please advise us* as soon as possible. If you didn't send a list of members last year, please do so now, including e-mail addresses and full mailing addresses for the mailing of WORLD NEUROLOGY.

For further information, please contact Keith Newton or Laura Druce at the WFN office in London at info@wfneurology.org. ■

A Call for Papers

The Journal of Nervous and Mental Disease, America's oldest continuously published independent monthly journal in the field, will celebrate its 200th volume in 2012.

John A. Talbott, M.D., the Editor in Chief, has announced that the anniversary issue will be dedicated to the History of Psychiatry and Neurology and has asked that submissions of papers of a historical nature (especially on subjects from 1974 to present) be submitted online by going to www.editorialmanager.com/jnmd.

These review articles should be between 4,400 and 8,800 words. The deadline for submission is Dec. 1, 2011. ■

‘The National’ Reflects on Its 150-Year Legacy

BY CHARLES CLARKE, MB, BCH, AND SIMON SHORVON, MB, BCHIR, M.D.

Few medical institutions today can show an unbroken record of development and achievement over more than a century and a half, as is the case with London’s National Hospital for Neurology and Neurosurgery. The National, as it is known worldwide today, began in a small house in 24 Queen Square, in 1860, when it was called the National Hospital for the Relief and Cure of the Paralysed and Epileptic. It was funded through the hard work, generosity, and broad charitable intent of many people, but especially a London family, sisters Johanna and Louisa Chandler and their brother Edward.

The siblings were orphans who lived with their grandmother. When she was paralyzed by a stroke, her grandchildren were struck by the lack of amenities for caring for her. After she died, the granddaughters began raising funds by making and selling bead and pearl ornaments. They raised £200 over 2 years before seeking input from the Lord Mayor of London, David Wire, himself partially paralyzed from a stroke.

The doors of that original building opened in 1860, while the present hospital, with the façade preserved to this day, was completed in 1890. Since then, it has delivered continuous service both to clinical neurology and, with the neighboring Institute of Neurology founded in 1950, to the experimental neurosciences.

The secret of the National’s achievements is essentially rooted in its commitment to assisting patients with neurological disease and the quality of its staff. The hospital also maintains a worldwide teaching role, offering courses to visiting fellows and postgraduate students from around the world. There has been the foresight to develop into areas of neurology that were less fashionable in the past, such as neurorehabilitation, stroke, headaches, and disorders of movement. At a scientific level, experimental work in neurophysiology, neurochemistry, and molecular genetics has blossomed, and more recently, in imaging prion diseases and mechanisms of neurodegeneration. Above all, the two institutions have maintained an emphasis on the needs of patients and on focusing on what they do best.

Photos courtesy National Hospital for Neurology and Neurosurgery

Joanna Chandler, left, and her sister Louisa, sold bead ornaments to raise funds for a hospital that could care for patients who had been paralyzed by stroke.

Many illustrious neurologists have served on the staff during its 150 years, including, during the first 100 years, Charles-Édouard Brown-Séquard, John Hughlings Jackson, William Richard Gowers, Victor Horsley, David Ferrier, Gordon Morgan Holmes, Samuel Alexander Kinnear Wilson, Francis Walshe, Charles Putnam Symonds, and Derek Denny-Brown.

In November 2010, the hospital held a study day as part of its 150th anniversary celebrations, reflecting the neurological and neurosurgical highlights of its history. A history of the hospital is to be recorded in a new scholarly book, *The National Hospital, Queen Square 1860-2010*, to be published in limited edition this year. It will complement the textbook in neurology by members of the hospital consultant staff (*Neurology: A Queen Square Textbook*, edited by Charles Clarke, Robin Howard R, Simon Shorvon, and Martin Rossor. Oxford: Wiley-Blackwell, 2009, 991 pp.)

Former students, staff and visitors at Queen Square are invited to join the Queen Square Alumnus Association. Membership offers many attractive benefits. Please contact alumnus@ion.ucl.ac.uk for further information or to register for membership.

► For information about the courses for visiting fellows and postgraduate students, write to: Institute of Neurology, Queen Square, London WC1N 3BG, United Kingdom; or e-mail education.unit@ion.ac.uk.

► To order a copy of the limited edition book of the hospital’s history at a prepublication offer (£45 plus postage), write to: National Hospital Development Foundation, Box 123, National Hospital, Queen Square, London WC1N 3BG, UK; e-mail NHDFFundraising@uclh.nhs.uk; or call +44-0-207-829-8724. ■

The National Hospital for Neurology and Neurosurgery has remained steadfastly committed to assisting patients with neurological disease and ensuring the quality of its staff, as well as offering training courses and pursuing research.

Dr. Clarke is honorary consultant neurologist at the National Hospital for Neurology and Neurosurgery, Queen Square, London. Dr. Shorvon is professor of clinical neurology at the Institute of Neurology, also at Queen Square.

Promise for Other Prion Diseases

Creutzfeldt-Jakob • *from page 1*

while the new biomarkers remain fairly stable in CJD-positive and CJD-negative cases,” the authors wrote (PLoS ONE 2011;6:e16804[doi:10.1371/journal. pone. 0016804]). None of the markers showed any correlation with age of the cases.

Diagnostic accuracy of T-TF, the TF isoforms, and T-tau was assessed using nonparametric tests, logistic regression, and receiver operating characteristic (ROC) area under the curve (AUC) analysis. Although T-TF was measured by both Western blot and enzyme-linked immunosorbent assay (ELISA), the Western blot results are deemed more accurate, because the ELISA test is optimized for measuring serum TF that lacks TF-beta-2 and is thus less accurate in measuring brain levels of T-TF.

Overall diagnostic accuracy was better with T-TF than with the individual TF isoforms, and better with each of the isoforms than with T-tau. Accuracy was improved over that with T-TF by using T-TF and T-tau together. The ROC AUC was 0.90 for T-TF and 0.93 for T-TF combined with T-tau. Values for the Akaike’s Information Criterion, which is used to compare different logistic regression models for different biomarkers alone or in combination and for which a lower value is superior, were 0.81 with T-TF and 0.70 for T-TF combined with T-tau.

With cut-offs defined to achieve a sensitivity of about 85% (based on the literature for biomarker comparisons in Alzheimer’s disease), T-TF identified CJD-positive cases with a specificity of 71.6%, positive likelihood ratio of 3.0, negative likelihood ratio of 0.2, positive predictive value of 81.7%, negative predictive value of 77.4%, and accuracy of 80.1%. The combination of T-TF and T-tau identified CJD-positive cases with a specificity of 87.5%, positive likelihood ratio of 6.8, negative likelihood ratio of 0.2, positive predictive value of 91.0%, negative predictive value of 80.0%, and accuracy of 86.2%.

The researchers noted that the study shows that CSF T-TF and the TF isoforms are superior to T-tau alone in identifying sCJD and suggests that the combination of T-TF and T-tau is superior to the currently used combination of T-tau and the biomarker 14-3-3.

There are additional advantages of CSF T-TF alone or in combination with T-tau as a potential diagnostic test for sCJD, which include:

► It is likely to be more specific for sCJD, because it reflects prion disease–associated brain iron imbalance.

► There is an opportunity for early diagnosis of sCJD, because there is a significant decrease in CSF T-TF at more than 12 months before end-stage disease.

► Consistent results can be achieved even in poorly preserved CSF samples, because TF is relatively resistant to limited degradation by proteinase-K.

► Levels of CSF TF are in the mcg/mL range, compared with the pg/mL range of T-tau and 14-3-3, which allows for accurate detection from a small sample volume without requiring pre-absorption of albumin and immunoglobulins.

► And CSF T-TF is quantifiable.

The authors concluded that their studies “provide confidence that CSF TF holds promise as a biomarker of sCJD. Evaluation of additional CSF samples from sCJD and other forms of prion disorders and comparison with cases of rapid-onset dementia will validate these observations further and probably lead to the optimization of current automated procedures for quantifying serum TF to CSF TF [ultimately providing] a quick and sensitive premortem diagnostic test for sCJD and other prion disorders.”

The authors had no conflicts of interests. The study was supported by funds from the National Institutes of Health. ■

NEUROLOGICAL HISTORY

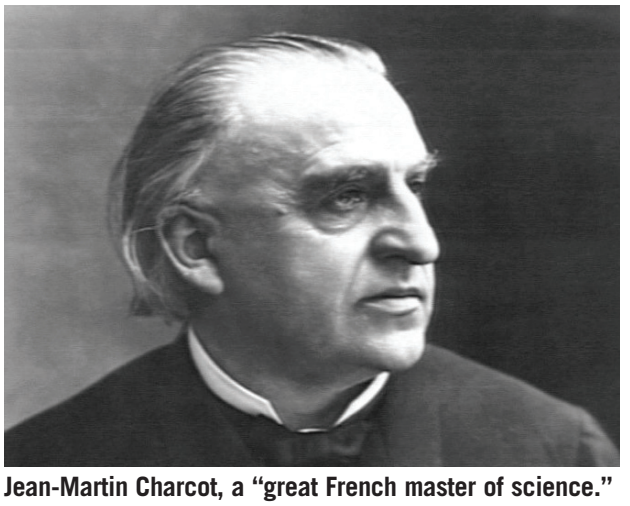
An American in Paris (and Other European Cities)

BY PETER J. KOEHLER, M.D., PH.D

Dr. Koehler is a neurologist in the department of neurology at the Atrium Medical Centre, Heerlen, the Netherlands. Visit his Web site at www.neurohistory.nl.

Between 1870 and 1914, many American students and postgraduates visited European cities to complete their medical training. William Osler, the distinguished Canadian clinician and medical educator, stated that German universities became the second home of all who loved science, scholarship, and truth.

Indeed, thousands of American, Russian, and Japanese physicians went to Vienna – which the American pathologist William Welch called the "conventional Mecca of American practitioners" (*American Doctors in German Universities*, TN Bonner. Lincoln: Nebraska University Press, 1963, pp. 1-21) – and Berlin to pursue popular courses in neurology that were often held in English.



Jean-Martin Charcot, a "great French master of science."

After Vienna and Berlin, Paris and London were also important centers for those wishing to train in neurology. Among these students was the American neurologist Bernard Sachs (1858-1944), who made a long European peregrination between 1878 and 1884. He studied under the German physicians Adolf Kussmaul, Friedrich von Recklinghausen, and Friedrich Goltz in Strasbourg, where he received his medical degree in 1882. He continued to Berlin, where he studied under Karl Westphal and where he likely also met Carl Wernicke; to Theodor Hermann Meynert in Vienna; Jean-Martin Charcot in Paris; and John Hughlings Jackson in London.

In his autobiography, Sachs recounted his experiences during his postgraduate studies with Meynert:

I began my postgraduate studies in Vienna in October of that year [1882] *under Meynert. At that time, Vienna, with its famous Faculty and its far-famed allgemeines Krankenhaus* [general hospital]*, was the mecca of all American students. The hospital and teaching arrangements were such that one could easily get special courses and special laboratory opportunities in any subject. While cerebral anatomy and neuropsychiatry were my especial aims and took up most of my time …*

But my chief purpose was to learn brain anatomy under Meynert – the great and most original brain anatomist. Great as a scientific investigator; but as a teacher, far from great. … Meynert and Westphal were great psychiatrists because they were also great neurologists. It would be fortunate if the young psychiatrists of the present day were trained in the same way, and not given certificates in psychiatry without the fundamental knowledge of organic neurology. …

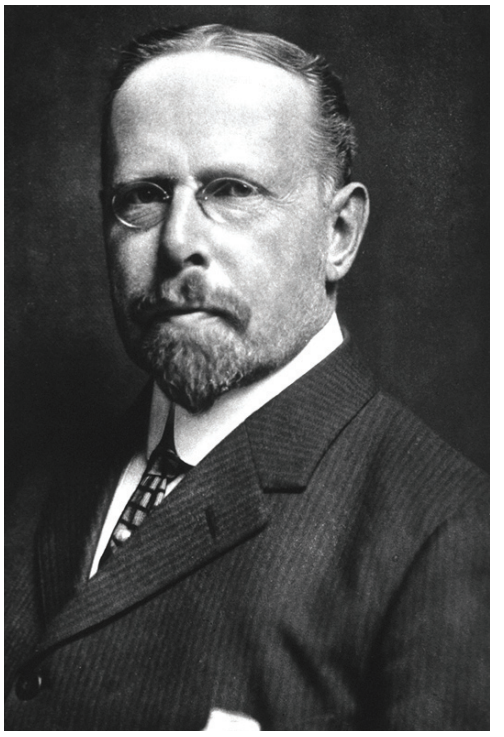
In the laboratory, I found myself in good company. Allen Starr was a hard and patient worker. … Both of us were ambitious and were equally devoted to the advance of neurology and psychiatry in America

[Sachs, B. Autobiography. New York, privately owned, 1949, p. 56].

Here, Sachs met several other students, some of whom became famous.

Starr, [Gabriel] *Anton, and I sat alongside of one another and close to Sigmund Freud, now by all odds the best known of the group. None of us suspected Freud's future fame. He pegged away at anatomy, as we all did, and although his doctrines took him far afield, in his last letter to me, written only a few months before his death, he acknowledged he had never severed his relations with organic neurology* [Autobiography, pp. 56-7].

Indeed, Sachs was not very pleased with the psychoanalytic movement, especially with respect to dystonic afflictions. In reaction to an explanation of mental torticollis presented by L. Pierce Clarke in 1914, Sachs said, "if this indicated the future trend for our present-day neurology, then the less we heard of it, the better."



Bernard Sachs received his medical degree in Strasbourg during his European travels.

Theodor Meynert, "great as a scientific investigator; but as a teacher, far from great."

PHOTOS COURTESY DR. PETER J. KOEHLER

Sachs compared Meynert with Charcot and Hughlings Jackson, both of whom he visited after his stay in Vienna.

I spent a number of months with Jean-Martin Charcot at La Salpêtrière in 1883. It was a great experience, after the dry and matter-of-fact teaching methods of German scientists, to revel in the more or less dramatic presentation and discussion of clinical phenomena by this great French master of science. All Frenchmen, even to the lesser Professors, seem to be possessed by a dramatic fervor. Every lecture at La Salpêtrière or at the Hotel Dieu [sic] *was as enjoyable as the average dramatic performance. I wish we British and American teachers of medicine had half the elegance of diction and half the skill in presentation of the average French instructor* [Autobiography, p. 57].

In the spring of 1883, Sachs stayed with Hughlings Jackson in London and made a comparison between his Viennese and London teachers:

It became very evident, after a few days, that like Meynert, Jackson was not an easy man to follow. … I determined to get at Jackson's medical thinking, and … followed closely Jackson's publications, especially on epilepsy and aphasia… for many years, Jackson's views influenced me more than did those of any other teacher with the possible exception of Kussmaul [Autobiography, pp. 58-9].

Sachs returned to New York in 1884, where he entered general practice and devoted himself to neurology and psychiatry, starting the translation of Meynert's *Psychiatrie*. ■

FROM THE JOURNAL OF THE NEUROLOGICAL SCIENCES

Study Highlights Dengue Role in Viral Meningitis, Encephalitis

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

Viral encephalitis and meningitis are uncommon but important diseases for two reasons: Encephalitis is often followed by very significant cognitive and motor deficits, which can be quite disabling; and both diseases can give rise to very extensive epidemics that can have a serious public health impact.

The recent epidemic of West Nile encephalitis in North America is a prominent example, but it was preceded by other epidemics in North America and elsewhere: the pandemic of HIV encephalitis in St. Louis, Missouri; encephalitis in the Midwest; Eastern equine encephalitis in Massachusetts; Japanese encephalitis in the Far East; and encephalitis lethargica from 1917 to the late 1920s in Europe and North America.

The effects of these diseases can tell us much about the basic biology of the nervous system. Thus, HIV encephalitis causes a subacute subcortical dementia, herpes encephalitis can change a patient's basic personality and cause an amnestic state, and encephalitis lethargica can result in a parkinsonian state.

It is important to understand the epidemiology of these diseases, because it provides considerable information about the public health importance of the disease as well as its basic biology. Thus, patterns of disease incidence and its spread can help identify ages of susceptibility and modes of dissemination.

Most epidemiologic studies have been done in temperate regions, where the countries tend to have the necessary expertise and infrastructure to manage these outbreaks. Thus, there is much data on the epidemiology of herpes encephalitis, HIV encephalitis, Eastern equine encephalitis, St. Louis encephalitis, and West Nile encephalitis in North America; but not for the less developed regions of the world.

The epidemiology of viral encephalitis and meningitis in South America has fallen under the latter scenario, but is now the subject of a paper by Brazil-based researchers led by Cristiane N. Soares (J. Neurol. Sci. 2011;303:75-9). The researchers prospectively collected data on patients who had been diagnosed with viral encephalitis and meningitis between March 2006 and March 2008 in a dengue-endemic area.

They recruited 81 patients; 37 met the diagnostic criteria for viral meningitis (20) and encephalitis (17). The researchers were able to determine the etiology of 85% of the meningitis and 76% of the encephalitis cases. These figures are impressive, since most previous studies were not able to diagnose any more than 50% or 60% of encephalitis cases.

This has implications for the pathogenesis of the infection. It is probably due to the high endemicity of dengue in the area, which is the most common cause of encephalitis. Thus, dengue can cause encephalitis if the virus is common enough.

Another example of the contribution of epidemiology to the understanding of the biology of viral infections arises from the meningitis series. The authors found that herpes simplex virus 1 (HSV-1) is a common cause of aseptic meningitis, second only to the expected enteroviruses. The association between HSV-1 and viral meningitis may reflect the site of latency in the lumbosacral roots, because HSV-1 is becoming an increasingly common cause of genital herpes, and therefore, the location of viral latency.

Further epidemiologic studies such as this are needed to give us information about the public health burden of these diseases, and to tell us about the basic characteristics of viral disease in humans. ■

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

Worldsleep2011
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New Horizons of Sleep Research for Our Planet

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Chair of Local Organizing Committee

KYOTO, JAPAN

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April 30, 2011

Deadline for Early Registration
June 30, 2011

Deadline for Advance Registration
September 30, 2011

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WFN JUNIOR TRAVELLING FELLOWSHIP REPORT

A Rich Line-Up of Presentations At Neuroscience 2010

I attended Neuroscience 2010, the annual meeting of the Society for Neuroscience, in San Diego, Calif., USA, last November as a World Federation of Neurology Travelling Fellow.

More than 35,000 neuroscientists attended the meeting, making it one of the world's largest forums for neuroscientists to debut their research findings and network with their international colleagues. The attendees included researchers; academics; undergraduate, doctorate, and postdoctorate students; and industry representatives.

BY ANURAG KUHAD, M.D.

Dr. Kuhad is in the Pharmacology Research Laboratory, University Institute of Pharmaceutical Sciences, at Panjab University, Chandigarh, India.

Several neuroscientists reported their latest research findings on neurodegenerative disorders such as Alzheimer's disease, parkinsonism and movement disorders, multiple sclerosis, pain, and depression in oral and poster presentation sessions.

A number of the lectures were particularly interesting. Prof. Yasmin L. Hurd of Mount Sinai School of Medicine, New York, spoke about the feasibility of studying discrete gene and protein expression in the brains of drug abusers to illuminate specific neurobiological features underlying addiction disorders. Dr. Yuh Nung Jan and Dr. Lily Jan from the University of California, San Francisco, delivered an informative lecture titled "Dendrites, From Form to Function." They summarized how dendrites form and organize among themselves, and how dendritic ion channels are regulated by synaptic activities and in turn modulate neuronal activity and synaptic plasticity; then they led a discussion on the implications of neurological diseases and mental disorders to etiology.

In another presentation, Dr. Mahendra Bishnoi, a postdoctoral fellow from Southern Illinois University School of Medicine, Springfield, USA, reported findings from a study on the effect of systemic and intrathecal administration of resiniferatoxin on nociceptive behavior in rats. The findings were encouraging because the role of different transient receptor potential vanilloid receptors in nociception in rats was being studied.

Apart from the scientific and technological presentations, there were a number that also addressed social and ethical issues. One such impressive talk was by Dr. Pawan Sinha of the Massachusetts Institute of Technology, Boston, USA, who spoke about Project Prakash, under which blind students in India are being treated and provided health care and education. Among the other issues discussed in this category were child poverty and human capital and conferring legal rights to animals in research.

At a very practical level, staff from the US National Institutes of Health ran workshops and discussions on writing research data and preparing manuscripts in accordance with the requirements of high-quality journals. I found another session on the mentor-mentee relationship very informative, especially on how to be an effective mentor.

Several companies demonstrated their newer technologies for the neuroscience lab, for example, the automated software-operated instrument for injecting drugs into different regions of the animal brain, a high-resolution confocal microscope for studying the different biomarkers of neurodegenerative disease pathologies, and electrophysiological equipment for tracking changes in ionic current alteration in neurodegenerative disorders.

I made many new contacts at the conference and learned much about my field, which I feel helped bridge the gaps in my knowledge and allowed me to return to India with novel ideas and valuable information that my colleagues and I can apply to our research. I was highly motivated after discussing my research findings on nociception in rats. ■

Afghan Physicians to Train in Pakistan

BY MOHAMMAD WASAY, M.D., AND PARVEZ NAYANI, M.P.H.

Aga Khan University in Karachi, Pakistan, and the American Academy of Neurology have signed a memorandum of understanding for two candidates from Afghanistan to train in neurology at AKU. The candidates will be internists or family physicians and after receiving 2 years of intensive neurology training, they will be able to practice as trained neurologists.

Afghanistan has been devastated by recurring wars over many decades, and the effects of this protracted turmoil are reflected in some of its key health indicators – an infant mortality of 129 per 1,000 live births, total life expectancy of 46 years at birth, two physicians per 10,000 population (out of a total population of 25 million).

Although there are 11 medical colleges and about 1,700 specialist doctors in Afghanistan, none of those institutions have neurology departments, neurology training programs, or trained neurologists on their staff or faculty. As such, large number of patients with neurological disorders travel to Pakistan, Iran, and India for diagnosis and treatment. Currently, all patients with neurological disorders are seen by family physicians, pediatricians, and internists, who not only have limited training in neurology but also lack the necessary equipment for neurological examination and diagnosis.

The AAN has started an Afghan Neurology Training Fund and has approved US$40,000 to fund the program, which is due to start May 1, 2011. Over the course of the 2-year program, trainees will learn about the diagnosis and treatment of common adult and pediatric neurological disorders as well as go through neuroradiology, psychiatry, and neurophysiology rotations.

In the second year, they will also learn how to set up and run a neurology training program. When the trainees have completed the program, they will return to Afghanistan, where they will be expected to establish neurology training programs at their home institutions. The AAN and the World Federation of Neurology will continue as advisers to the trainees on their return to Afghanistan. ■

Dr. Wasay *is professor in the department of neurology at Aga Khan University, Karachi, Pakistan, and* Mr. Nayani *is the director of the French Medical Institute for Children in Kabul, Afghanistan.*

Calendar of International Events

2011

9th Congress of European Paediatric Neurology Society
May 11-14
Cavtat/Dubrovnik, Croatia
www.epns2011.com

20th European Stroke Conference
May 24-27
Hamburg, Germany
www.eurostroke.eu/

European Neurological Society 21st Meeting
May 28-31
Lisbon, Portugal
www.congrex.ch/ens2011

15th International Congress of Parkinson's Disease and Movement Disorders
June 5-9
Toronto, Canada
www.movementdisorders.org/congress/congress11/

European Neuro-Ophthalmology Society Meeting
June 18-21
Barcelona, Spain
www.eunos2011barcelona.com/

15th Congress of the International Headache Society
June 23- 26
Berlin, Germany
www2.kenes.com/ihc2011/pages/home.aspx

8th International Brain Research Organisation World Congress of Neuroscience
July 14-18
Florence, Italy
www.ibro2011.org/site/home.asp

4th Congress of the Pan-Asian Committee for Treatment and Research in Multiple Sclerosis
Aug. 25-27
Kyoto, Japan
www.pactrims.org

29th International Epilepsy Congress
Aug. 28-Sept. 1
Rome, Italy
http://www.epilepsyrome2011.org/

World Congress on Huntington's Disease
Sept. 11-14
Melbourne, Australia
www.worldcongress-hd2011.org/

20th World Congress of Neurology
Nov. 12-17
Marrakesh, Morocco
www2.kenes.com/wcn/Pages/Home.aspx

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IS APPROVED...

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Clinical Neurology News

— We Write Medicine's First Draft —

www.clinicalneurologynews.com

Genetic Insights May Guide Pediatric Stroke Therapies

BY JEFF EVANS
Elsevier Global Medical News

Primary and secondary prevention measures for children at risk for idiopathic arterial ischemic stroke need to target disease mechanisms unique to nonatherosclerotic arteriopathies, according to pediatric stroke researchers.

Risk factors, signs, and symptoms differ for arterial ischemic stroke (AIS) in adults and children. Early recognition of factors unique to at-risk children can prompt initiation of prophylactic treatment with antiplatelet drugs, anti-inflammatory drugs, and anticoagulants when thrombosis and inflammation play important roles in the pathogenesis, Dr. Pinki Munot of Great Ormond Street Hospital for Children NHS Trust, London, and coauthors wrote in a review (Lancet Neurol. 2011;10:264-74).

Many of these arteriopathies appear to be caused by single-gene mutations that affect various parts of an artery's structure at different points in its development, homeostasis, or response to environmental stress, offering a range of different targets for research.

To detect the underlying genetic disorder, Dr. Munot and colleagues advised asking about clinical history of stroke, migraine, porencephaly, learning difficulties, and static motor disorders, and to look for disease in vascular beds outside the brain. They recommended pursuing genetic investigations only in patients with cerebrovascular and noncerebrovascular features that are suggestive of a genetic cause.

The authors described how single-gene mutations contribute to known phenotypes described in various pediatric cerebral arteriopathies (not including inherited metabolic disorders).

Vascular Development

The deletion of a region of chromosome 7 that contains the gene for elastin (ELN) causes Williams-Beuren syndrome. Arteriopathy in most cases of the syndrome (70%) results in supravalvular aortic stenosis but can involve other vascular beds, and causes an overgrowth of smooth-muscle cells. Occlusive disease most often results from the overgrowth of smooth-muscle cells caused by the lack of elastin; aneurysmal disease has not been reported.

ACTA2, the gene for a member of the highly conserved actin proteins, actin alpha 2, codes for a main contractile protein in vascular smooth-muscle cells. Mutations affecting it result in dysfunctional smooth-muscle cell contraction and the proliferation of smooth-muscle cells that occlude smaller arteries but seem to make larger arteries vulnerable to aneurysmal disease. A diverse number of vascular beds can be involved, which is most noticeable in the fact that all mutation carriers have livedo reticularis.

Homeostasis and Remodeling

The Notch signaling pathway is essential in determining the differentiation of smooth-muscle cells and their response to vascular injury. Mutations in NOTCH3 and JAG1 genes affect this pathway.

NOTCH3 mutations lead to arterial wall thickening and stenosis in mostly small vessels in the condition called CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy). Most reports of cerebral infarction have been reported in adults but might be underrecognized in childhood.

The jagged-1 surface protein encoded by JAG1 is mutated in nearly 90% of individuals with Alagille syndrome. Individuals with this syndrome appear to harbor abnormally thin-walled vessels with myointimal hyperplasia of the vascular wall. Occlusive and aneurysmal arterial disease observed in the syndrome are associated with ischemic and hemorrhagic strokes.

Dysregulation of transforming growth factor beta (TGF-beta) signaling caused by mutations in the gene coding for HtrA serine peptidase-1, HTRA1, is known to result in the condition called CARASIL (cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy). The disease causes a dysfunction in vascular homeostasis, resulting in diseased cerebral small arteries, which usually arises in adulthood. They show arteriosclerosis with intimal thickening and dense collagen fibers, loss of vascular smooth- muscle cells, and hyaline degeneration in arterial media. Other features of CARASIL such as alopecia can begin in adolescence. Mutations in genes for TGF-beta receptors, TGFBR1 and TGFBR2, cause Loeys-Dietz syndrome, which is characterized by arterial tortuosity and large-vessel, noncerebrovascular aneurysmal disease. In arterial tortuosity syndrome, the loss of function of a facilitative glucose transporter encoded by SLC2A10 (or GLUT10) leads to defective collagen, elastin, or both, and activates TGF-beta as a secondary response to a defective extracellular matrix.

THE EARLY RECOGNITION OF FACTORS UNIQUE TO AT-RISK CHILDREN CAN LEAD TO THE PROMPT INITIATION OF PROPHYLACTIC TREATMENT.

Abnormal vascular homeostasis in pseudoxanthoma elasticum, caused by a mutated ABCC6 gene, leads to a calcification of elastic fibers and might be seen with cutaneous signs in childhood, though it is most often diagnosed in teens and young adults when AIS and peripheral vascular disease become prominent.

Persons with mutations in the pericentrin gene PCNT that cause the autosomal recessive disorder microcephalic osteodysplastic primordial dwarfism type II (MOPD II) have an emergent and progressive cerebrovascular disease in childhood such as moyamoya syndrome and, less often, aneurysmal disease that support a role of the centrosomal protein pericentrin in vascular homeostasis. The mutations also cause vascular disease in many areas outside of the cerebral circulation in individuals with MOPD II, which is characterized by microcephaly, pre- and postnatal growth failure, skeletal dysplasia, and dysmorphism.

The rare, nonatheromatous arteriopathy called moyamoya usually causes bilateral occlusive disease of the terminal internal carotid arteries and is considered one of the most severe childhood cerebral arteriopathies. The overproliferation of smooth-muscle cells in the syndrome, with colocalization of inflammatory cells such as macrophages and T cells, is "probably genetically mediated," said the authors. But genotype-phenotype correlations have been difficult because of varying degrees of precision used to describe moyamoya in the literature. "Identification of single-gene disorders associated with moyamoya might lead to a better understanding of childhood cerebral arteriopathy," because the disorder "often represents one aspect of a more diffuse arteriopathy."

Response to Injury

Stroke phenotypes in some single-gene disorders have been associated with physical trauma to the head or neck, abnormal inflammatory response, or oxidative injury. A range of phenotypes has been associated with mutations in the gene that encodes the alpha-1 chain of type IV collagen, COL4A1. It reduces the stability of vascular basement membranes and can lead to idiopathic small-vessel disease in children, including occlusive and aneurysmal cerebral arteriopathies associated with ischemic and hemorrhagic stroke phenotypes. Cerebral hemorrhage in individuals with COL4A1 mutations might be associated with trauma, based on a study that identified trauma to the head or neck in the preceding 2 weeks as a risk factor in previously healthy children.

A mutated form of SAMHD1 is one of five genes that have been associated with the encephalopathic syndrome called Aicardi-Goutières. Children with this mutation had cerebral arteriopathy with either occlusive or aneurysmal features, peripheral vascular disease, which shows that "as with ACTA2-related disease, the skin can indicate the presence of cerebrovascular disease."

Excessive smooth-muscle cell proliferation and vascular occlusion occur in individuals with neurofibromatosis type 1 (NF1), which is caused by mutations in the NF1 tumor-suppressor gene. NF1 normally inhibits activity of the Ras signaling pathway, but its disinhibition results in intimal proliferation, smooth-muscle nodules, and fibrosis of the vascular media and adventitia. About 6% of children with NF1 have diffuse cerebral arteriopathy with features of occlusive and aneurysmal disease. Evidence suggests that chronic inflammation is an important factor in NF1 arteriopathy, but the trigger for this is unclear.

Mutations in ATP7A, in X-linked recessive Menkes disease, affect copper transport. These present with varying phenotypes and degrees of severity. The disorder mainly causes connective-tissue abnormalities but can cause a progressive neurodegenerative disorder that results in death in infancy. Ischemic and hemorrhagic stroke, structural abnormalities in cerebral arteries, oxidative injury, and energy failure have been reported with the vascular phenotype.

Abnormal Metabolites

The X-linked lysosomal storage disorder called Fabry's disease is caused by a deficiency of alpha-galactosidase that arises from mutations in the GLA gene that encodes the enzyme. The metabolite globotriaosylceramide builds up in vascular endothelium, causing injury and progressive arteriopathy in large and small vessels. About 40% of hemizygous men develop stroke with vessel ectasia.

The autosomal recessive disorder homocystinuria leads to a deficiency in cystathione-beta synthase and an increased risk of stroke and abnormal blood clots. These effects of hyperhomocysteinemia are suspected to occur through a dysfunction of the vascular endothelium and procoagulation effects. The authors had no financial conflicts to report. ■

Child Stroke Scale Validated

For the first time, a pediatric stroke severity scale has been validated in a prospective clinical trial.

The study in 15 North American medical centers showed excellent interrater reliability when neurologists used the Pediatric NIH Stroke Scale (PedNIHSS), a pediatric version of the National Institutes of Health Stroke Scale for adults, to examine 113 patients aged 2-18 years with acute arterial ischemic stroke, Dr. Rebecca N. Ichord, director of the pediatric stroke program at the Children's Hospital of Philadelphia, reported at the International Stroke Conference in Los Angeles.

The patients were examined daily from admission to discharge, or day 7 of hospitalization.

Interrater reliability was tested in a subset of 25 patients who underwent simultaneous examinations by two pediatric neurologists. Characteristics of the subgroup were similar to those of the entire cohort. The simultaneous raters' scores were identical in 60% of ratings and were within a 1-point difference in 84% of ratings (Stroke 2011;42:613-7).

–Sherry Boschert

A video interview with Dr. Ichord about the scale can be viewed using the QR code (see p. 14), or go to www.clinicalneurologynews.com, click on the video icon, and search for "Pediatric Stroke Severity Scale Validated."

Child Neurology Association's Global Education Plan

Progress in pediatric neurosciences is proceeding rapidly, and we are entering an era in which technologies will allow for a greater knowledge and understanding of normal and abnormal brain development. Because of our improved diagnostic abilities, it is now possible to identify even subtle brain abnormalities early on, thus allowing for early intervention. However, in certain areas of the world, many children do not benefit from this progress because of the shortage of child neurologists and adequately equipped medical centers.

In recent years, this progress in diagnostic and therapeutic capabilities and the growing necessity for advanced technology to diagnose CNS disorders have greatly increased the divide between developed and developing countries. In addition, child neurologists from developing countries are hampered by the lack of professional networks that could provide continuous education and updates on new developments in the specialty.

About 70% of children with disabilities live in resource-poor countries, and most of them have neurological diseases. Protein-energy malnutrition, dietary micronutrient deficiencies, environmental toxins, and a lack of early sensory stimulation may contribute to the high prevalence of neurodevelopmental disabilities in these countries. Access to up-to-date imaging and genetic and biochemical testing is limited in some regions, which is particularly problematic because delaying diagnosis and treatment can have deleterious effects on a child's development.

There is an urgent need to identify regional centers and reference labs to improve diagnosis of neurological disease in children in developing countries. In Central Asia, the number of qualified child neurologists has increased in recent years, but they are not equally distributed between urban and rural areas, with about 95% of them concentrated in the countries' capital cities. The situation is worse in Africa, where many countries have no child neurologists at all.

Education is one of the primary goals and purposes of the International Child Neurology Association (ICNA). The ICNA Education Committee has organized numerous programs for improving participants' knowledge of pediatric neurological disorders at the primary care level and for promoting clinical research interest in child neurology. In the past decade, these clinically oriented events have focused on comprehensive aspects of child neurology and have been organized in several countries, including Egypt, Estonia, Guatemala, India, Kazakhstan, Kenya, Peru, Ukraine, and Uruguay. The main goals of these events were to improve the use of relevant diagnostic measures and management in pediatric neurological care, and enrich the teaching and academic skills of local trainers.

Under the ICNA educational programmes, a number of different strategies have been adopted to promote education in emerging countries. Among these was for the ICNA executive board to hold its annual meeting in conjunction with local or regional child neurology organizations in different countries or regions, and for the association to provide speakers and scientific support to local conferences. In doing these things, ICNA has had a significant impact on the development of regional child neurology associations in Asia, Africa, Eastern Europe, the Middle East, and South America.

BY PAOLO CURATOLO, M.D.

Dr. Curatolo is professor of pediatric neurology at Tor Vergata University, Rome, and a former president of the International Child Neurology Association.

In 2002, my administration established research as the top prerogative of our society. Not surprisingly, ICNA's primary research priority is to document and define the causes of neurological handicaps in children in various geographic regions so that approaches to prevention and treatment can be tailored to a region's specific needs.

We urgently need to build this research capacity in emerging countries through international cooperation so that we are united against the devastating neurological disorders that affect millions of children worldwide. ICNA has a unique role in improving international cooperation and promoting clinical and scientific research by providing a medium through which physicians can exchange opinions at an international level for the advancement of pediatric neurosciences.

The Internet is the key to coordinating global education in pediatric neurology. ICNA supports a Web site, www.icnapedia.org, that provides access to pertinent papers, clinical guidelines, consensus statements, and management protocols. The association is deeply committed to providing innovative educational and training programs for all professionals involved in the care of children with neurological disorders. Its International Education Committee plans to develop a distance learning course in pediatric neurology for those who are not able to travel to attend courses and conferences in person.

ICNA is uniquely qualified and well positioned to remedy this deficit by reducing the gap and increasing the level of child neurology care all around the world. To accomplish this ambitious goal, ICNA should work with the World Federation of Neurology and World Health Organization. This international cooperation is more important than ever to promote brain health globally. ■

Part of this article is adapted from a paper by Dr. Curatolo that appeared in the Journal of Child Neurology (2010;25:1444-9).

Cultural Differences Could Inform Migraine Therapy

BY MATTHEW STENGER
Elsevier Global Medical News

An appreciation of sociocultural differences in knowledge of migraine triggers and symptoms and migraine treatment may result in improved management of migraine, according to findings from a study conducted in Spain and Brazil.

Researchers led by Francisco Carod-Artal, from the neurology departments at Virgen de la Luz Hospital, Cuenca, Gregorio Marañón University General Hospital, Madrid, and University Hospital, Valladolid, Spain, showed substantial differences in reported triggers of migraine and frequency and types of treatment between migraineurs in Spain and those in Brazil.

Recent data indicate a 1-year gender- and age-adjusted prevalence of migraine of 15.2% in Brazil and a 1-year prevalence of 11.0% in Spain (15.9% in women, 5.9% in men). In the current study, 292 patients were consecutively recruited over a 4-month period from one Brazilian and two Spanish neurology outpatient clinics (141 and 151 patients, respectively). All of the patients were from urban environments and were of middle socioeconomic class. They had to have primary headache and a neurologist's diagnosis of migraine to be included. Mean ages were 33.1 years for Brazilian migraineurs and 35.9 years for Spanish migraineurs, and 81.6% and 78.1%, respectively, were female. The age at first migraine was 17.5 years in Brazilian patients and 19.8 years in Spanish patients. Family history of migraine was more common in the Brazilian patients (79.4% vs. 64.3%, $P = .004$).

Brazilian patients had a greater mean number of migraine attacks during the preceding month (7.3 vs. 3.8, P less than .001). Migraine with aura was reported by 41.3% of Brazilian patients and 34.0% of Spanish patients, with visual aura being the most frequent aura type (80.7% of all cases), followed by sensory aura. The most common symptoms of migraine overall were photophobia (83.2%), phonophobia (82.2%), and nausea (78.4%). Significantly more Brazilian patients reported nausea (90.8% vs. 66.9%) and vomiting (68.8% vs. 22.6%), whereas photophobia (84.4% vs. 82.1%) phonophobia (86.5% vs. 78.2%), and headache aggravation during physical activity (75.2% vs. 68.2%) were reported by similar proportions of Brazilian and Spanish patients.

Significantly more Brazilian patients identified migraine triggers (79.4% vs. 66.2%, $P = .01$). Overall, sleep disturbance and stress were the most commonly reported triggers. Brazilian patients reported food (30.5% vs. 12.6%, $P = .0002$), sleep disturbance (56.7% vs. 28.5%, P less than .0001), smells/odors (52.5% vs. 9.3%, P less than .0001), stress (73.1% vs. 46.4%, P less than .0001), and, among women, menstruation (55.6% vs. 38.1%, $P = .02$) as triggers with significantly greater frequency.

Differences in Treatments, Preventive Medications

For treatment of acute migraine attacks, analgesics (aspirin, acetaminophen) and anti-inflammatory drugs were used by 98.2% of Brazilian patients and 87.5% of Spanish patients (P not significant). Ergotamine was used by 4.6% and 7.1% (P not significant), respectively, but significantly more Spanish patients used triptans (16.3% vs. 47.0%, P less than .0001).

There were also major differences between populations in terms of use of preventive medication: 52.9% of Spanish patients used preventative medicine, compared with 21.9% of Brazilian patients (P less than .0001); significantly more Spanish patients used anticonvulsants (28.5% vs. 2.8%), antidepressants (24.5% vs. 10.6%), beta-blockers (20.5% vs. 5.7%), and calcium channel blockers (19.2% vs. 8.5%).

Brazilians 'Undertreated'

The findings show that "Brazilian migraineurs are more often undertreated for migraine, [with] underutilization of triptans and preventatives [being] observed," the authors wrote (J. Neurol. Sci. 2011 [doi:10.1016/j.jns.2011.02.027]. "The differences found in symptom frequency (such as nausea and vomiting, often related to pain intensity) and susceptibility to triggers may be partially explained by a lesser use of triptans in treating acute attacks in our Brazilian series and a significant difference in the use of preventatives."

Triptan use was greater in Spanish patients even though they had a significantly lower mean number of acute attacks, with this latter fact likely related to the greater use of preventive medication by Spanish migraineurs. The greater recognition of migraine triggers among Brazilian patients may be related to the increased frequency of acute attacks associated with the reduced use of preventive treatments.

Other data from an urban headache center in Brazil indicate a wide use of vitamins/herbal therapies (24%) and nonmedicinal therapies (32%) for migraine in Brazil, perhaps accounting for the underuse of efficacious preventive drugs observed in the current study. Differences in medication use between the populations may be explained by additional sociocultural differences or differences in access to particular medications; such factors were not investigated in the current study.

The authors reported that they had no conflicts of interest and no source of financial support. ■

Delay in Antiretroviral Delivery

South Africa • *from page 1*

which contrasts with the high yields of 69% smear and 87.9% culture positivity rates in a Vietnam study.[7] Molecular studies improve the yield of a positive diagnosis, but there is an unacceptable false-negative result rate.[4] Findings from a recent local study examining an interferon-gamma T cell ELISPOT assay, hold promise for the rapid immunodiagnosis of TBM.[8]

An added burden has been the emergence of multidrug and extensively drug-resistant (MDR and XDR, respectively) TB, and now total drug-resistant (TDR)

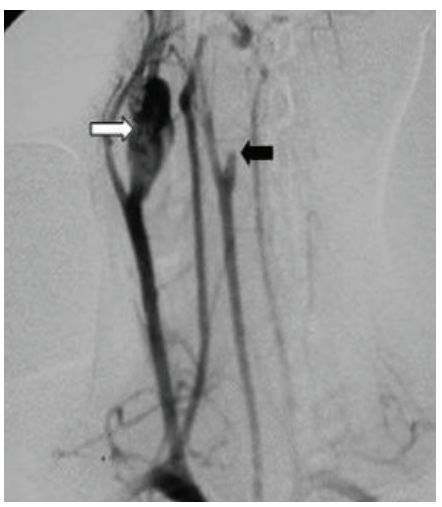


Figure 2. A carotid angiogram showing an aneurysm on the left (white arrow) and an occlusion (right, black arrow).

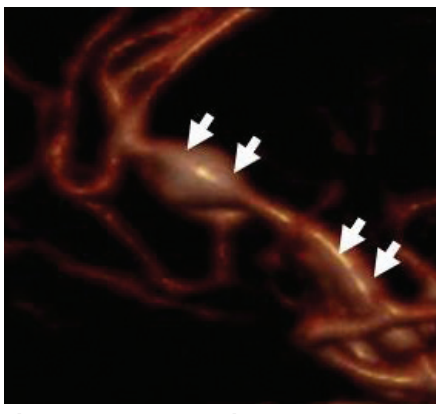


Figure 3. An MR angiogram of the intracranial vessels showing fusiform aneurysmal dilatation (arrows).

TB. South Africa has the fourth-highest number of MDR TB cases in the world.[3] A knock-on effect has been the development of MDR and XDR TBM with devastating results.[9] Conventional confirmation by culture and sensitivity of MDR or XDR TBM is hopelessly prolonged and patients have usually died by the time their drug-resistant disease has been confirmed. Molecular techniques that include drug resistance in their assays have been shown to be useful in sputum samples. A study is currently underway in our unit to evaluate the role of these tests in the CSF.

► **Intracranial tuberculomas** are common in HIV-positive patients and behave like any other intracranial mass, though unlike with other masses, they are seen in patients with higher CD4 counts.

► Myelopathy may occur as **spinal tuberculosis – or Pott's disease** – or craniospinal meningitis. Other presentations include multiple intramedullary tuberculomata and epidural tuberculous abscesses (see Figure 1) without bony involvement.[10] These latter presentations were seldom seen in the pre-HIV era.

Cryptococcal Meningitis

Cryptococcal meningitis continues to be a major problem in HIV-positive patients, with mortality in those admitted in a disturbed state of consciousness approaching 100%. Visual loss is a major problem despite aggressive attempts to lower intracranial pressure.

An added problem is the limited availability of amphotericin B in the rural areas. In these instances, we recommend high-dose fluconazole – for example, 800 mg daily – for 6-10 weeks, depending on the response, then followed by maintenance therapy. Some studies have safely used daily doses as high as 1,200-1,400 mg.

Intracranial Mass Lesions

The causes of intracranial mass lesions (IMLs) in HIV-positive patients are similar to those reported in developed countries, except that the intracranial tuberculomata are more common.[11] Another peculiar observation is that intracranial abscesses tend to be multiple and more than one organism may be isolated from a single abscess cavity. A primary source of infection is usually not identified, and the prognosis of these patients is uniformly poor. The standard treatment for toxoplasmosis is sulfadiazine and pyrimethamine; however, sulfadiazine is not available locally. My colleagues and I undertook a prospective study using a high dose of cotrimoxazole as sole therapy with excellent results.[12]

Spectrum of Myelopathies

The spectrum of myelopathies is wide and includes the usual causes, such as tuberculosis, syphilis, herpes simplex, herpes zoster, and unexplained myelitis.[10] KwaZulu-Natal, a province in South Africa, is a human T-lymphotropic virus Type I (HTLV-I) endemic area. A number of patients therefore present with dual HIV and HTLV-I infections.

The cause of the myelopathy in the dually infected patients is thought to be from the HTLV-I rather than HIV, because most patients do not have features of symptomatic HIV infection, such as weight loss, candidiasis, or multiple organ disease. Dually infected patients present with myelopathy at an earlier age compared with those infected with HTLV-I alone. There is some evidence that coinfection accelerates the progression of each virus to clinical disease.

Patients with syphilitic myelopathy have shown an excellent response to intravenous penicillin. Zoster myelitis may occur coincident with the cutaneous lesion or several weeks later. When my colleagues and I originally did a study of myelopathies in HIV-positive patients,[10] we rarely saw vacuolar myelopathy. With the advent of ARVs, patients are surviving longer and cases of vacuolar myelopathy, which emerges in the late stages of HIV infection, are seen more frequently.

Cerebrovascular Disease

Strokes related to tuberculosis and syphilis because of endarteritis are easily explained. However, a peculiar large vessel extracranial vasculopathy has been responsible for cerebral or limb ischemia in HIV-positive patients. Aneurysms and stenoses occur (Figure 2) and, in addition, there is an isolated intracranial aneurysmal vasculopathy (Figure 3) that presents either as ischemia or subarachnoid hemorrhage. However, extensive investigations have failed to reveal a secondary cause, suggesting HIV may be the etiologic factor.

Parainfectious Disorders

► **Acute disseminated encephalomyelitis** is poorly documented in the literature, but is not a rare diagnosis[13] (and unpublished data). Patients present with major neurological deficits, but with adequate support and no specific therapy apart from steroids in some of the cases, most of them show significant improvement. The usual investigations to find other triggers for acute disseminated encephalomyelitis have been uniformly unrewarding. The better prognosis contrasts with that seen in the viral exanthems, where the fatality rate may vary from 5% (varicella) to 25% (measles).

► **Chronic inflammatory demyelinating neuropathy** is seen in two to three HIV-positive patients each year. The clinical and investigative profiles are identical to those of HIV-negative patients, except that there is also a mild lymphocytic CSF pleocytosis. Sural nerve biopsies show inflammatory infiltrates and varying degrees of demyelination and axonal degeneration. Patients show a good response to steroids. It could be argued, however, that in some cases, HIV status may be incidental given the infection's high prevalence.

Miscellaneous Disorders

► **Immune reconstitution syndrome** is the exacerbation of the clinical or radiological features of a pathogenic antigen not due to relapse or recurrence. Much is made of neurological IRIS, but the condition is not common. Furthermore, in the pre-HIV era, one saw similar paradoxical reactions when initiating specific therapy.

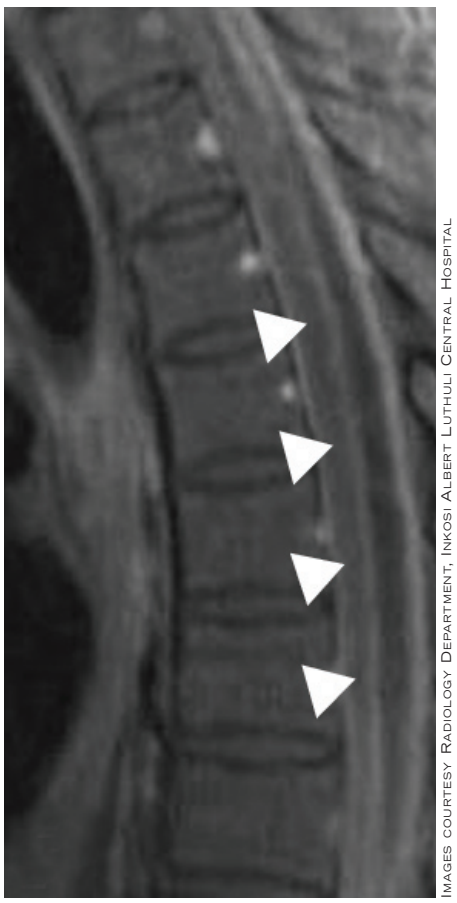
► **Progressive multifocal leukoencephalopathy** (**PML**) has a global prevalence of 4%-7%, but for reasons that are not clear, it is less prevalent in South Africa. There are no good population-based data of the frequency of the virus in South Africa. Findings in one study[14] found that 60% of HIV-positive individuals without PML have JC virus DNA in the peripheral blood. (The virus causes PML.) My colleagues and I have not been able to confirm this in patients in an ongoing study.

► **Painful distal sensory neuropathy** (**DSP**) was seen intermittently in state hospitals before the ARV rollout, but the disorder markedly increased after the rollout because stavudine was part of the initiating regimen. Patients with drug-induced DSP are otherwise well, but present with a disabling neuropathy with dysesthesia and hyperpathia. As of 2010, stavudine, which was also responsible for deaths from lactic acidosis, has been replaced with tenofovir.

Conclusion

There has been a renewed initiative by the government of South Africa to make ARVs widely available. More than 1 million individuals are estimated to be on antiretroviral drugs – the highest number in the world. Although commendable, this is only about 40% of the patients who are eligible for therapy. The potential pool of patients who require ARVs has been further increased by new guidelines stipulating that anyone with a CD4 count of less than 350 should be offered therapy.

The ARV roll-out will bring problems of its own such as side effects and the possible emergence of resistant HIV strains because of poor compliance. But health care providers hope the roll-out will lead to a better quality of life for HIV-positive patients and a decrease in mortality and in opportunistic infections. ■



IMAGES COURTESY RADIOLOGY DEPARTMENT, INKOSI ALBERT LUTHULI CENTRAL HOSPITAL

Figure 1. Sagittal MRI scan of the spinal cord with an epidural tuberculous abscess (arrows). Note there is no bony disease.

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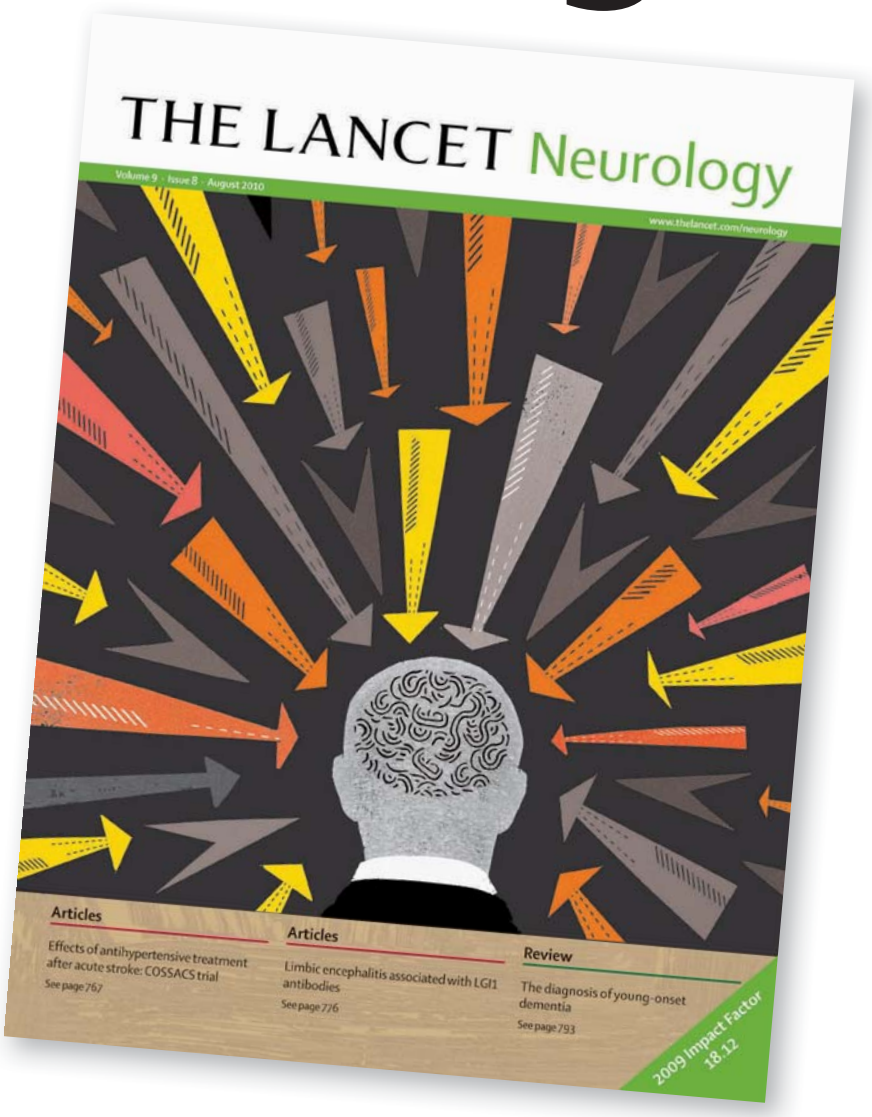

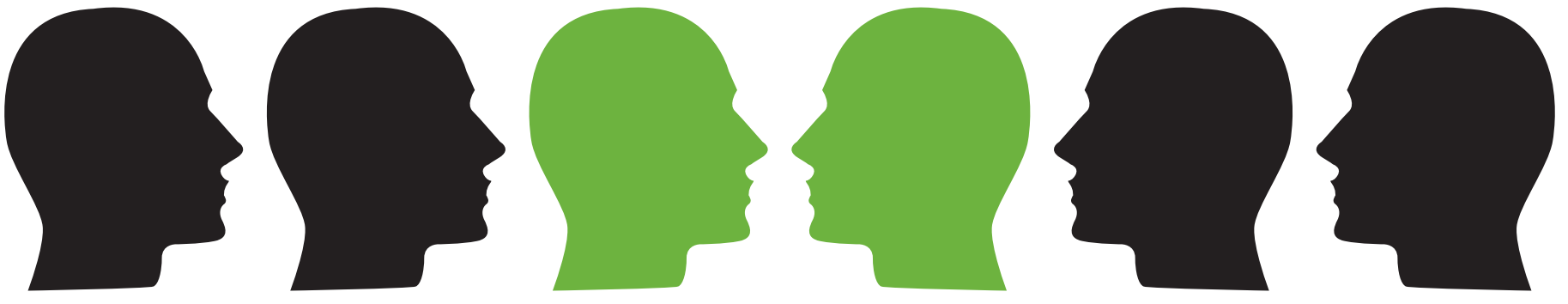

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BOOK REVIEWS

A Comprehensive Work on Focal Neuropathies

***Focal Peripheral Neuropathies* (4th ed.)**
By John D. Stewart
West Vancouver: JBJ Publishing, 2010, 700 pp.

BY MARK HALLETT, M.D.
Editor in Chief, WORLD NEUROLOGY

I had to review this book. It has a tribute to Asa Wilbourn, now deceased, who was an expert in electromyography and peripheral neuropathies and who reportedly said he preferred an earlier edition of this book to his own book. By that I presume he meant the third edition of *Entrapment Neuropathies*, which he coedited with me and David Dawson after we invited him to fill in for the late Lewis Millender, who had worked with us for the first two editions. Never having read any of the earlier editions of *Focal Peripheral Neuropathies*, I thought it was time.

Every neurologist should have a book on focal peripheral neuropathies. Thomas Willis, the 17th century English doctor who coined the term neurology, meant it to be the study of the peripheral nerves, so from a historical point of view neurologists should be experts in this field. But neurology training often emphasizes central nervous system disorders, and some of the neuropathies are uncommon and forgettable. It is comforting and valuable to have a source of this information at hand.

The idea of writing a book on entrapment neuropathies was originally that of Thompson and Kopell (*Peripheral Entrapment Neuropathies* [1st ed.]; Walter A. L. Thompson and Harvey P. Kopell; Baltimore: Williams & Wilkins, 1963), but it was long out of date, which was what motivated Dawson, Millender, and me to write the first edition of *Entrapment Neuropathies* (Boston: Little, Brown, 1983). The first edition of Stewart's *Focal Peripheral Neuropathies* came out in 1987. The general notion of focal peripheral neuropathies is broader than entrapment neuropathies, but entrapment is likely the most frequent etiology. Thus, books formally on either topic have largely overlapping material.

Focal Peripheral Neuropathies has the obligatory chapters on anatomy and pathology, but the meat is in the chapters on the individual nerves, individual roots, and the brachial and lumbosacral plexes. (Who doesn't need a handy reference on the brachial plexus?) Each chapter begins with a description of the anatomy and then discusses the pathologies. The individual pathologies are discussed in detail and accompanied by a comprehensive review of the literature on each. There are many illustrations of patients showing the distribution of sensory loss and muscle wasting. Some figures are rather artistic, such as one of a right-sided suprascapular neuropathy in a patient with a large tattoo on the upper back. Most of the figures are original; some are borrowed, including from *Entrapment Neuropathies*; and there is a beautiful illustration of the pattern of sensory loss in a patient with mononeuritis multiplex from Churg-Strauss syndrome taken from Richard Rosenbaum and José Ochoa's book, *Carpal Tunnel Syndrome and Other Disorders of the Median Nerve* (Boston: Butterworth-Heinemann, 2002).

Stewart also discusses laboratory evaluation, including electrodiagnosis, but this is not the place for the electromyographer to learn the details of technique. Therapy is discussed, again on the background of a comprehensive literature review, but it is also not the place for learning about the details of surgical procedures that are undertaken for some entrapments.

The field is full of controversial topics such as the thoracic outlet syndrome, resistant tennis elbow, and the piriformis syndrome, all of which are approached thoughtfully and sensibly and summarized with personal opinions. I agreed with them all.

There are occasional typographical errors and very rare factual errors, such as, in different places, ascribing the origin of the accessory deep peroneal nerve to the deep and superficial peroneal nerves; the latter is correct (though the peroneal nerve is now preferentially called the fibular nerve). This is a particularly good and comprehensive book. Its emphasis differs somewhat from that of *Entrapment Neuropathies*, and it is certainly much more up to date. And, while I cannot go as far as my coeditor, Asa, I am happy to have a copy. ■

Case-Based Examples, Expert Reviews Inform and Advise

Companion to Peripheral Neuropathy: Illustrated Cases and New Developments
By Peter James Dyck, Kimberly Amrani, Christopher J. Klein, P. James B. Dyck, Phillip A. Low, JaNean Engelstad, and Robert J. Spinner
Philadelphia: Saunders Elsevier, 2010, 432 pp.

This fine book opens with a fascinating foreword by Arthur K. Asbury, M.D., emeritus professor of neurology at the University of Pennsylvania, Philadelphia, USA, in which he details how Guillain-Barré syndrome came to be associated with autoimmunity and explores the role of the GBS animal model, experimental allergic neuritis.

The book is laid out in four sections: MRI-targeted fascicular nerve biopsy, diagnostic case reports, autonomic disorders, and scientific reports, each of which is highly informative and worthwhile reading.

In the first section, neurologists and neurosurgeons will see what a tremendously valuable technique MRI can be for diagnosing diseases involving the peripheral nervous system. The authors provide many excellent cased-based examples consisting of illustrated computed tomography images and the corresponding nerve pathology.

The section on diagnostic case reports includes a large series of very different cases. In each, the clinical presentation suggests a specific diagnosis. Certain particularities, however, give the clinician cause to consider other diseases in the differential diagnosis, leading to relevant changes in the patients' specific diagnosis and therapy. The cases chosen by the different authors are invariably instructive and well documented, and the discussions clearly portray the strategies used in each scenario to approach and reach the diagnosis. It is extremely informative to read these cases carefully and to understand the thinking behind each one. This same recommendation applies to the autonomic disorders section, which affords practical, stimulating, and rewarding reading.

BY ISABEL ILLA, M.D

Prof. Illa is chief of the neuromuscular diseases unit in the department of neurology at Hospital Santa Creu i Sant Pau, Universitat Autònoma de Barcelona, Spain.

The final section on scientific reports is a must-read, because each of the invited authors has succeeded in the difficult task of summarizing their many years of knowledge on each of the subjects chosen. (In addition to Dr. Dyck and his coauthors, all from the Mayo Clinic in Rochester, Minn., USA, there is an impressive list of 146 distinguished contributors.)

The book is available online and contains valuable references to current literature in the field. ■

Treating Mild Stroke Could Save Patients, Cut Costs

The use of clot-busting drugs in patients with mild stroke could save thousands of them from long-term disability, and about US$200 million a year in stroke-related costs.

In deciding whether to administer tissue plasminogen activator (tPA) to patients with mild stroke, one must balance the possible benefits with the risk of further bleeding, Dr. Pooja Khatri said at a press briefing at the International Stroke Conference in Los Angeles. But her epidemiologic study of 150 mild strokes – of which 4 were treated with tPA – suggests the drug could prevent the disability that affects up to one-third of these patients.

Of 441 patients treated for ischemic stroke during 2005, 56% (247) had mild strokes. Of those, 62% (150) were considered eligible for tPA treatment, but only 1% (4) received the drug.

Dr. Khatri, of the University of Cincinnati Academic Health Center, did not follow the patients to compare clinical outcomes over time. However, she said, based on two extant studies, about 30% of mild stroke patients experience deficits that affect their lives.

She extrapolated her findings to the entire U.S. population in 2010, estimating that mild strokes would have occurred in 27,203 patients without baseline disability. If all had received an effective treatment, up to 13% (3,761) could be saved from disability.

The U.S. National Institutes of Health sponsored the study. None of the reseachers had any disclosures.

–Michele G. Sullivan

View a video of Dr. Khatri by using the QR code, or go to www. clinicalneurologynews. com, click on the video icon, and search for "Treating Mild Strokes Could Yield Benefits."

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BOOK REVIEW

Lessons and Reflections on the tPA Debate

tPA for Stroke:
The Story of a Controversial Drug
By Justin A. Zivin and
John Galbraith Simmons
Oxford University Press USA,
2010, 208 pp.

This book presents a review of the discovery, development, testing, and implementation of recombinant tissue plasminogen activator for treating stroke patients. As the subtitle implies, it is intended to be a factual account of that history and also an exposé.

The "controversy" is the failure of the medical community, including stroke specialists, neurologists, emergency physicians, government regulators, and Genentech (the company that developed the drug in the United States) to appropriately accept, promote, and use what the authors forcefully and convincingly argue was a groundbreaking and effective new treatment for the most common neurological disease and cause of adult disability.

Of particular relevance to the WORLD NEUROLOGY readership was (and still is) the failure of the neurological community in this regard, which should be enough to make most conscientious neurologists squirm when reading those portions of the book. The authors save their most pointed criticisms for those leaders of the emergency medicine specialty who used misinformation and non–peer-reviewed opinion pieces to attempt to discredit studies by researchers at the National Institute of Neurological Disorders and Stroke (NINDS), an affiliate of the U.S. National Institutes of Health (NIH).

The book is easy to read, is carefully referenced and indexed, and was researched by conducting personal interviews (portions of which are reproduced as direct quotations) with most – but not all – of the key players involved with tPA and stroke. Although the book is written at a technical level that the lay audience can easily understand, it contains sufficient detail and facts to be of interest to any clinician or scientist interested in this topic.

Patient Stories Convey the Message

There are actual patient stories that bring home the human message of why the appropriate use (and unfortunately, frequent nonuse) of tPA is so critically important; and the facts contained in the book, with a few relatively minor exceptions, are accurate. Specifically, I found the chapter on how the drug was discovered and initially developed, and another on the economic issues that affect its use, particularly well done.

My main criticism of the book is also in some respects one of its strengths, that is, the review is very "Zivin-centric." Dr. Zivin was and still is a key figure in the development and implementation of tPA for stroke. Although the drug would eventually have been tested and proven effective for stroke without him, there is no question that he had the intelligence and combination of clinical and scientific knowledge to appreciate the potential of tPA at a time when few knew about it, and those who did, thought it would never be a safe or effective treatment for stroke. He had the perseverance to obtain the drug from its discoverers and Genentech, and to obtain funding from the NIH and NINDS to carry out the initial animal studies that demonstrated its effectiveness and safety; and then he had the forcefulness to lobby strongly for its clinical testing and, eventually, its use.

There are probably only a few other individuals who could provide as authoritative perspective or who played as important a role in the development of tPA for stroke.

Unfortunately, some of those other people and their opinions are not adequately represented in the book. In particular, there is very little mention of others, some of whom Dr. Zivin probably considered competitors, who were pivotal in the early testing of thrombolytics for stroke. These would include Dr. Hermann Zeumer of Germany, who did the first thrombolytic procedures using an endovascular approach; Dr. Gregory Del Zoppo of the United States, who followed the early work of Dr. Zeumer and eventually helped lead studies that paralleled the NINDS studies; and Dr. Etsuro Mori, who carried out a clinical evaluation of tPA in Japan essentially at the same time the NINDS studies were starting.

THE BOOK IS A WAKE-UP CALL FOR PEOPLE TO UNDERSTAND THE IMPORTANCE OF BEING FULLY INFORMED ABOUT EFFECTIVE STROKE CARE.

There is also insufficient recognition that the first European study of intravenously administered tPA (ECASS-1) began at the same time as the NINDS studies and in fact was completed first; and although the findings were not positive, they certainly trended in the direction of success and imbued the entire stroke research community with optimism.

What set the NINDS studies apart, and what led to their success, was how they differed from these other studies in certain important aspects, including their short time window (half of the patients were enrolled within 90 minutes of stroke onset time; the other half within 180 minutes); the dose-finding preliminary study; the careful selection of investigators; the protocol development entirely by investigators without influence from marketing and pharmaceutical company interests; and the careful statistical and administrative oversight by Dr. Barbara C. Tilley, Dr. K. Michael Welch, and Dr. John Marler. All of these points are accurately identified and emphasized in the book.

BY JAMES C. GROTTA, M.D.

Dr. Grotta is professor and chair of the department of neurology and director of the vascular neurology program at the University of Texas Medical School at Houston.

Releasing vs. Withholding Findings

So it is somewhat surprising that Dr. Zivin takes strong issue with the conduct of the NINDS studies, in particular the failure to release the part 1 results when that portion of the study was completed.

Dr. Zivin obviously felt and still feels very strongly about this point, enough to generate a personal postscript explaining his position. This is perhaps the most interesting part of the book for the stroke specialists who were involved in the NINDS studies or for readers who are interested in the details of their conduct.

Dr. Zivin argues forcefully that withholding the results of part 1 until the completion of part 2 was one reason for the failure of the medical community to accept the final results of the trial, and he criticizes NINDS leadership and the studies' data and safety monitoring board (DSMB) for providing too much "top-down" direction, rather than using the traditional investigator-driven approach that would have required interruption of the study after part 1, publication of its results, and reapplication and peer review of part 2.

A Different View

My own view is the opposite, and Dr. Zivin does not consider any alternate view in his postscript. In fact, the investigators did not want their research interrupted between the two parts if it appeared that they were headed in the right direction, which the DSMB recognized was the case after its review of the part 1 data.

It was labor intensive to develop and maintain the clinical infrastructure at each site to allow recruitment of patients within 90 minutes of symptom onset, and required funding both for extra nursing personnel (another unique aspect of the NINDS study which is not widely enough recognized as contributing to its success) and for constant communication between the investigators and their hospital emergency department and emergency medical service partners. Any interruption between part 1 and part 2 would have led to the decay of these carefully developed networks, and there was no guarantee that they could be re-established. The "seamless" progression from part 1 to part 2 saved time and resources.

Furthermore, contrary to Dr. Zivin's assertion, I think it would have been highly unlikely that the U.S. Food and Drug Administration would have approved tPA for stroke on the basis of part 1, which was not designed as a pivotal efficacy study, had fewer than 300 patients, and was not positive for its primary end point.

Finally, the oversight of the studies by the independent data board and NINDS leaders in my opinion was key to the success of the studies by keeping them on track.

When the DSMB saw that part 1 was not positive on its prespecified 24-hour primary outcome measure, but was positive on most other prespecified secondary measures, including the most critical for proving efficacy – 3-month outcome – they encouraged the investigators to immediately begin a pivotal second trial to prove the effect at 3 months. NINDS leadership facilitated the continuation of funding to enable this to happen.

Importance of Being Educated

Imagine if the same neurologists who inappropriately attacked the results of the NINDS studies after their eventual publication had been on the study section that would have had to review a part 2 protocol after the results of part 1 were published!

I do agree with Dr. Zivin that instead of combining the results in a single brief article in the New England Journal of Medicine, it would have been better to release the part 1 data earlier, after part 2 was underway. That would have made it more evident that the NINDS studies were in fact two separate studies and perhaps made the final results appear more convincingly confirmatory.

In summary, despite the quibbles I have just listed, *tPA for Stroke* serves as a loud and effective wake-up call to the public to understand why they are still not likely to get effective stroke care unless they are fully informed. If they read this book, they will be informed consumers and will know the importance of recognizing stroke symptoms, acting immediately, and getting the stroke patient to an appropriate stroke center.

It is indeed a sad commentary on our health care system that such a book is needed. ■

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