Add-On Therapy Might Reduce Sudden Epilepsy Deaths

Randomized trials show that adjunctive antiepileptic drug treatment of patients with previously uncontrolled seizures is associated with 83% lower odds of sudden, unexpected death, according to a meta-analysis of placebo-controlled studies.

Dr. Philippe Ryvlin of the Hospices Civils de Lyon (France) and his coauthors in the meta-analysis suggested that their “findings offer hope and guidance in the prevention of SUDEP (sudden unexpected death in epilepsy) by indicating that an intervention can reduce the incidence of this devastating outcome.”

But the researchers noted that some experts dispute the clinical relevance and value of adding additional antiepileptic drugs (AEDs) to prevent SUDEP. SUDEP is the main cause of death in patients with refractory epilepsy, based on an incidence of 3.5 to 9.3 per 1,000 person-years. Risk factors include the frequency of seizures (particularly secondary generalized tonic-clonic seizures) and subtherapeutic levels of AEDs.

While bringing seizures under control might prevent a significant number of SUDEP cases, there is a lack of controlled studies evaluating interventions. The meta-analysis performed by Dr. Ryvlin and his associates compared the incidence of definite, probable, and possible SUDEP in patients with uncontrolled partial or primary generalized tonic-clonic seizures who received AEDs at efficacious doses vs. those who received placebo. They also compared these against deaths from other causes and the total number of deaths between the two groups (Lancet Neurol. 2011;10:961-8).

The researchers searched the Medline and Cochrane Library electronic databases and other...
Integrating Disease Prevention Into Medical Practice

Is there a need for a paradigm shift in the way neurologists practice? The traditional approach is to heal the sick. We wait for someone to get sick and come to us before we intervene. And, indeed, this is also the model for physician payment. One message from the World Congress of Neurology was that this model for medical care is likely not sufficient or the most effective. It is certainly better to prevent infectious disease than to treat it after it has developed. Public health measures can deal with the spread of many of these agents through improving sanitation, control of vectors such as mosquitoes, and vaccination campaigns. Some news about infectious disease at the Congress was frightening. Polio is on the rise. An increasing percentage of tuberculosis is treatment resistant. Will there be new diseases such as HIV and West Nile virus? The idea that we are good at treating infectious disease is certainly limited. Clearly, there are ongoing efforts in Africa to deal with some of this, but more disease is certainly limited. Those who treat infectious disease is definitely limited. Clearly, there are ongoing efforts in Africa to deal with some of this, but more disease is certainly limited. Clearly, there are ongoing efforts in Africa to deal with some of this, but more...
PRESIDENT’S COLUMN

The End of the Beginning

Half a century ago, Sir Winston Churchill, the prime minister of Britain, said, “Now this is not the end. It is not even the beginning of the end. But it is, perhaps, the end of the beginning.” We have begun the changes by redefining our mission, which now states that the World Federation of Neurology (WFN) is to “foster quality brain health worldwide.”

Now that the different committees of the WFN have defined their priorities, there will be an invitation to the WFN membership to join the activities of their interest.

We have developed standards by which we work, particularly as a team, and we have also established for the first time an opportunity for members of the WFN to submit applications for funding for special projects, which have been funded primarily by the WFN but also with input from other organizations, including the World Stroke Organization (WSO) and the International League Against Epilepsy (ILAE).

For 2012, we plan to invite another round of grant applications for funding for projects. We also plan to change the structure of the Grants Review Committee, which I have chaired, to include members of brain and neurology organizations that share common interests with us and may join us in co-funding projects.

At the World Congress of Neurology in Marrakesh, Morocco, in October, Gustavo Roman, chair of the Latin American Initiative, called for a meeting to explore the desirability and feasibility of establishing a Pan-American Federation of Neurological Societies. The meeting is to be chaired by Ana Robles, the Regional Director for Latin America, and the decisions from that meeting will be presented at the 13th Pan American Congress of Neurology in La Paz, Bolivia, March 4-8, 2012.

Other changes in 2012 will be the appointment of a new Editor of the Journal of Neurological Sciences to succeed Dr. Robert Lisak (USA). The current Editor of WORLD NEUROLOGY, Mark Hallett, will complete his innovative and distinguished term in 2012, and an advertisement inviting applications for the position is on page 15 of this issue.

At an international level, the Federation plans to continue building the World Brain Alliance to devise a world brain agenda to raise awareness of the importance of global brain health at the World Health Organization and the United Nations as well as with national and regional governments.

The World Brain Alliance is an organization of 10 international societies. It will hold a brain summit meeting in London, England, in 2014 to coincide with the planned European Brain Year.

Our plans are ambitious, times are hard, and we anticipate that great effort will be needed if we are to achieve our goals. However, if our track record to date is anything to go by, we know that change is possible, especially if it is a result of planned evolution rooted in a solid foundation that provides a sound basis for continuity.

Let 2012 be the year of your greater involvement with the World Federation of Neurology. I wish you and your families a happy New Year!

Continued from previous page

importance of brain health. Dr. Hachinski said that there was to be a summit meeting at the current WCN of all the neurology subspecialty organizations, also in an effort to establish cohesion and synergies. Dr. Hachinski also described the WFN’s Pilot Projects Program, under which 14 projects will be started or facilitated around the world. A new round of proposals will be called for shortly.

Vladimir Hachinski, MD

Delegates heard presentations on the WFN’s many activities and enjoyed a sneak preview of the new Web site.

Vice President Werner Hacke reported that he has been involved in planning for the 2011 Congress as well as the 2013 Congress in Vienna and the early evaluation phase of sites for the 2015 Congress, which was discussed later in the meeting. The Education Committee cochair, Stephen Serrag and Wolfgang Grisold, reported that the committee was active in supporting teaching programs, visiting professorships, and travelling fellows; the distribution of Continuum, an educational product from the American Academy of Neurology; and assisting with the arrangements for African neurologists to train in Turkey. Dr. Hachinski, who oversees the Applied Research Groups, said that she has been in liaison with these groups and other subspecialty societies in neurology. She noted that groups “come and go,” and that a new group focusing on disorders of consciousness is being formed.

Alfred Njamshi, the Pan-Africa Regional Director, gave an important report on the African Initiative, a major focus of WFN activity that began during the presidency of Johan Aarli. He emphasized educational initiatives.

Training is improving in many centers on the continent, and opportunities are arising for African neurologists to train elsewhere in Africa as well as countries outside of Africa. There are fellowships for African neurologists to attend meetings around the world, including the WCN, and three regional meetings were sponsored by the European Federation of Neurological Societies, the International Brain Research Organization, and the WFN. Amadou Gallo Diop of Senegal spoke about the use of “neurocaravans” to facilitate the education of local health care workers and delivery of neurological care in isolated areas. The neurocaravan is a van that transports neurologists into the country for several days at a time during which they conduct consultations and can even do EEGs.

Ryuuji Kaji, an WFN Elected Trustee from Japan, spoke about the Asian Initiative. In addition to supporting local neurological meetings and the Asian Oceanean congresses, the group is trying to help smaller countries establish neurological associations. Gustavo Roman, an Electored Trustee from the USA, reported on the Latin American Initiative, noting upcoming educational activities and local meetings, including the PanAmerican Congress.

WFN Secretary-Treasurer General Raad Shakir gave his report, which included approval of the minutes of the last council of delegates meeting and discussion of the finances. The auditors were reappointed by vote. Dr. Shakir noted that there are currently 113 WFN member societies. Moldova had been approved for membership by the Membership Committee and was admitted into membership in the WFN by unanimous vote of the Council. The next action was voting for an Electored Trustee. The candidates were Gustavo Roman, running for re-election, and John Wokke. Dr. Roman was successful in his bid.

The final part of the discussions dealt with upcoming World Congresses. The 2013 Congress will be in Vienna, and the organization committee is already working developing the scientific and social programs. The business of the current meeting was to vote for the site of the 2015 Congress, specified to be in the Americas. Dr. Francisco Cardoso of Brazil and Dr. Renato Vergudo Latorre of Chile presented the bids for the 2015 Congress on behalf of their respective countries. Dr. Shakir and Dr. Hacke gave their site visit reports and Kenes, the Congress organizers, reported on the technical aspects of the sites. After much discussion, Chile received the most votes and will likely host the 2015 Congress, pending successful negotiation of price for use of the congress center.

Following this vote, there being no further business, the meeting adjourned.
I
n 1929, the Swedish neurologist Sa-lomon Henschen (1847-1930), known for his research in aphasia and the reti-nal and cerebellar system, planned an Academia Neurologica Internationals to promote cooperation between inter-national neuroscientists. Letters between Henschen and the neurologists Cécile and Oskar Vogt, who at the time were at the Kaiser Wilhelm Institute for Brain Research in Berlin-Buch, Germany, sug-gest that a great number of international-neuroscientists supported the project. The Vogts were Henschen’s most im-portant partners in the project; Cécile would take over the office of secretary and as a person of French origin, was to expand the French as well as the inter-national framework.

An Erudite Body

Henschen hoped that the academy would serve as a revival of the Interna-tional Brain Commission, which had been founded in London in 1903 under the patronage of the International As-sociation of Academies. Between 1906 and 1912, some brain research institutes were accredited through the commis-sion, including those of Paul Fleisch (Leipzig), Heinrich Obersteiner (Vienna), Constantin von Monakov (Zurich), Lud-wig Edinger (Frankfurt am Main), Wladimir Bechterew (St. Petersburg), Cornelius Ubbio Ariens Kappers (Amster-dam), and Karoly Schaffer (Budapest).

By 1915, more than 50 high-ranking sci-entists, Henschen among them, were members of the commission and two, Ramón y Cajal and Camillo Golgi, were Nobel laureates.

Although many of Henschen’s es-teemed colleagues initially were enthu-siastic about the project, it was not nec-essarily an indication that they would participate in the conference. After nu-merous endorsements, Henschen arranged a provisional program of pa-pers and discussions. As an old and sick-ly man – he was 82 at the time – he planned to spend his remaining years es-tablishing a sustainable institution. How-ever, within 2 months (March-April 1929), the number of active conference participants decreased so that the provi-sional program had to be revised a num-ber of times. Moreover, the intended headquarters location in the Netherlands had to be transferred to Stockholm after Henschen’s Dutch colleagues (Bernardus Brouwer, Kappers, and Cornelius Wi-nkl) opposed the formation of an inter-national body. The Germans remained loyal to Henschen. The invitation for the conference from 28-30 May, 1929, had hardly been printed when the conference had to be called off because of the death of international attendees.

Was Henschen’s designation of the organization as an academy too am-bitious and might the term “conference” have been more appropriate? The pro-posed program was actually just that and thus it could not function as a re-placement for the Brain Commission. There were other obstacles:

▶ Brouwer, Kappers, and Winkler be-lieved that an academy could only be cre-ated as a national institution by a state and could not become a supranational organization.

▶ von Monakov was convinced that the

A Failed Bid to Revive the Early Brain Commission

BY BERND HOLDORFF, MD

Brazilian Researchers Take on Dengue Fever

BY CRISTIANE SOARES, MD, PhD

Brazil is the largest country in South America, with a pop-ulation of just under 191 mil-lion. Given its tropical and sub-tropical region climates and population demographics – an aging population and social in-equality – it is no surprise that dengue fever, malaria, and yel-low fever are endemic problems.

Brazil has the most areas en-zoic for yellow fever on con-tinental America. It is endemic in the impoverished northern region of the country and emerges sporadically as epi-demic/endemic in the central western region.

Since 2000, it has been spread-ing progressively beyond its usu-al boundaries and into areas that were formerly known as en-zoic. The last urban outbreak of yellow fever in Brazil oc-curred in the city of Ipatinga in 1998.

Despite 1930s of intensive ef-fort to control malaria, the dis-ease remains a major cause of morbidity in Brazil. The most recent available data are for 2008, when 314,420 slide-con-firmed malaria cases were re-port ed countrywide, 99.9% of which were acquired in Amazonia. About 52% of malaria cases oc-cur among adults older than 20 years. These data repre-sent 57.4% of all clinical malaria cases reported in the Americas and the Caribbean. It is still not clear why malaria remains so difficult to control in Brazil.

As a neurologist, I am part of a research team led by Dr. Marzia Puccioni-Sohler, work-ing in the CSF Laboratory at Hospital Universitario Clementino Fraga Filho in Rio de Janeiro, Brazil. We study neurological infections, using CSF analysis. Our focus is on viral infections of the central nervous system, especially the dengue virus.

Clinical neurological re-search is also done at the neu-roinfection ambulatory service of the Federal Hospital dos Servidores in Rio de Janeiro. The coordinator of the ambu-latory clinic selects patients for clinical and CSF studies. Our neu-rology residents learn how to investigate and treat patients who pre-sent with a range of dif-ferent neuroinfections.

We are particularly interested in viral meninitis and en-cephalitis because their etiology was unknown in HIV seropositive adults living in our re-gion. This lack of information is very common in developing countries since almost all studies on the epidemiology of these diseases have originated in coun-

tries in the northern hemisphere. Thus, we sought to determine if tropical areas in Brazil have viral prevalence similar to countries in Europe or North America. It came as a surprise to us that dengue virus was the main cause of encephalitis.

For future studies we are planning to work with dengue viral load in patients who pre-sent with neurological manifesta-tions that have been caused by dengue virus.
BEFORE THE RESEARCH IS PUBLISHED...

BEFORE THE DRUG IS APPROVED...

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Update on Africa

Lecture titled, Stroke: The Global Agenda, as did Vladimir Hachinski in his presidential lecture on Hypertension and the Brain. Vice President Werner Hacke, also speaking in the Presidential Symposium, emphasized the challenges ahead in implementing preventative NCD measures: an increase in population, an aging the population, discrepancies in the distribution of resources, and the increasing costs of medical care. He also noted that prevention is critical for moving forward successfully.

The status of neurology in Africa was reviewed during an excellent session sponsored by the Pan African Association of Neurological Sciences (PAANS). The speakers were Adesola Ogunnyi of Nigeria, Gilbert Dechambenoit, a neurosurgeon from the Ivory Coast, Charles Newton of Kenya, and Alfred Njamnshi of Cameroon. They listed a number of problems that hampered neurological practice in Africa, including the small number of neurologists and their maldistribution in favor of urban areas and to the detriment of remote rural areas, the dearth of training programs, and the significant treatment gaps because of the unavailability of medications for diseases such as epilepsy. The prevalence of other NCDs such as epilepsy, migraine, and Alzheimer’s disease are increasing. However, there are some solutions that are being put in place. Education is increasing, thanks in part to WFN efforts together with the European Federation of Neurological Societies and the International Brain Research Organization. Traditional healers, to whom many patients go first, are now beginning to work with physicians. Telemedicine is also beginning to have an impact on the delivery of care, especially to remote regions, and this could be considerably expanded with modern technology. Dr. Njamnshi emphasized the effectiveness of the TEAM approach. Together Everyone Achieves More.

In addition to the talks by President Hachinski and Vice President Hacke during the Presidential Session, the Moroccan Society of Neurology’s Mostafa El Alaoui Faris, President of the WCN 2011, spoke about the neuropsychology of the Arabic language. Lord Walton of Detchant, President of Neurology’s Mostafa El Alaoui Faris, President of the WCN 2011, spoke about the neuropsychology of the Arabic language. Lord Walton of Detchant, President of the World Congress of Neurology in Vienna, Sep. 22-27.

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Vladimir Hachinski and his wife Mary Ann, and Gallo Diop (Senegal) and his wife Fatou.

Mostafa El Alaoui Faris, WCN 2011 president, and Khadija Al Zemmouri of the local organizing body.

Guests at the opening ceremony of the Congress received a warm welcome to the host city by Moroccan performers and singers (above).

WFN President Vladimir Hachinski’s address focused on hypertension and the brain.

Bill Carroll (Australia; left) and Alan Barber (NZ).

Mostafa El Alaoui Faris, WCN 2011 president, and Khadija Al Zemmouri of the local organizing body.

Past WFN presidents, Johan Aarli (Norway; left) and James Toole (USA).

Yomi Ogun (Nigeria) delivered a paper on the epidemiology of neuro-HIV in Africa.

Keith Newton, the London-based Executive Director of the WFN.
Suggested Algorithm for Tuberculous Meningitis Might Help Streamline Diagnosis

T
he burden of tuberculosis and its complications is largest where the need is greatest. In many of the world’s regions, resource-poor environments bear the burden of tuberculosis disease with their limited resources to manage such epidemics. The TB-HIV syndemic has compounded this problem and has increased the number of new and recurrent TB patients.1 Last year, the World Health Organization (WHO) recorded about 7.8 million new and recurrent pulmonary TB (PTB) cases, of which about 850,000 were extrapolmonary tuberculosis (EPTB). A large proportion of those cases were in sub-Saharan Africa, the Eastern Mediterranean, and South-East Asia.2 In TB and HIV endemic populations, a significant number of patients have EPTB, of which 5%-18% have tuberculous meningitis (TBM).

TBM is a difficult diagnosis to confirm or exclude, given the low yields for microscopy and culture seen in routine laboratory processing. A cerebrospinal fluid (CSF) volume of less than 6 mL and a 30-minute examination within 60 minutes of the sample being taken are factors that are known to improve the yield for microscopy,3 but are not always possible because of the human resource and workload constraints in endemic settings. Attempts to define predictive factors for TBM have consistently identified a history of symptoms for more than 5 days, CSF lymphocyte predominance, CSF glucose below 2.2 mmol/L, or a CSF-blood glucose ratio of 0.5.

If an HIV-positive patient presents with a meningitic illness and a week-long history, then a CSF lymphocytosis, a negative cryptococcal latex agglutination test, a CD4 count of more than 200 cells/mm3, and a CSF-blood glucose ratio of 0.2 are, together, predictive for TBM. However, neutrophil predominance (15% of cases) and a normal CSF-blood glucose ratio (about 30% of cases) may be seen. There is a greater occurrence of neutrophilia in HIV-positive individuals, possibly because of a compromised adaptive arm but a relatively well-functioning innate arm. Normal CSF findings have also been described in these patients. In those cases in which CSF findings are normal, a reliable test to confirm or exclude TBM as a meningitic etiology is required.

Test Specificity, Sensitivity Varies

Various attempts using liquid culture media such as PCR (sensitivity, 56%; specificity, 95% confidence interval, 0.46-0.66; and specificity, 98%; 95% CI 0.97-0.99),5 as well as antigen and antibody tests (sensitivity, 56%; sensitivity range, 0.26-1.00; and specificity, 98%; specificity range, 0.59-1.00),5 have not realized their promised potential. Yields for the microscopic observation drug susceptibility assay (MODS), when compared with those of the Mycobacteria Growth Indicator Tube (MGIT) and Lowenstein-Jensen media (sensitivity, 52.6%, 64.9%, and 70.2%, respectively), may be promising for quicker results.6 Newer tests, such as antigen-specific region of difference interferon-gamma response assays (IGRAs), may hold promise and have been shown to have a specificity and sensitivity of 82% (95% CI, 66-92) and specificity of 100% (95% CI, 78-100) cut point, equal to or greater than 46 spot-forming cells). CSF interferon-gamma levels hold similar promise in TB and HIV endemic populations. The accompanying figure suggests a diagnostic algorithm for TBM, in patients from TB and HIV endemic environments. Application in different populations is required to confirm the utility of this algorithm.

When CSF changes are atypical, or if patients present with clinical meningitis after already having been on TB therapy for TB elsewhere in the body, or with immune reconstitution inflammatory syndrome (IRIS), the pathogenesis of clinical meningitis may be difficult to elucidate. There is an increased risk for IRIS in HIV-positive patients with low CD4 counts. In a patient with possible IRIS, there may be an emergent TBM, alternative etiology, or unmasking of existing TB infection in the CSF space. Management of such patients varies from stopping TB therapy to adding steroids to the existing regimen. This is largely empirical, however, a recent randomized, controlled trial showed benefit for steroid use.7 Hydrocephalus and basal enhancement may support TBM in appropriate populations; however, this may occur less frequently in HIV-positive individuals.

Regarding TB therapy, 9-12 months of initial therapy with four drugs (rifampicin, isoniazid, ethambutol, and pyrazinamide), followed by two drugs (rifampicin, isoniazid) are recommended. Therapy for multidrug resistant (MDR) TBM and extensively drug-resistant (XDR) TBM is largely empirical. Moxifloxacin may hold promise as it has good CSF penetration and has been found to achieve adequate minimum inhibitory concentrations.8

In HIV-positive patients on TB therapy who develop CNS symptoms, management is uncertain, as it is when patients present with possible IRIS. In one study, investigators recorded a frequency of 19% of patients with neurologic TB-IRIS, of whom 23% had paradoxical TB-IRIS.9 Exclusion of alternative etiologies and steroids is currently recommended.

Poverty a Factor in Prevalence

Complications such as hydrocephalus occur in up to 70% of patients, more often in children and less so in HIV-positive individuals. Devastating cerebrovascular incidents occur in about 60% of patients, according to findings in MRI-based studies.10 Therapy to prevent cerebrovascular incidents is uncertain. Other complications include spinal myelitis and arachnoiditis with significant morbidity. TBM remains a devastating illness, particularly in TB- and HIV-endemic environments that have poor resources, and studies relating to the pathogenesis of complications with emphasis on specific management would be valuable. Further studies on optimal therapy for MDR and XDR therapy in TBM are also needed. Finally, I would add that a very important aspect in the reduction of TBM prevalence is poverty alleviation, as this would help with both the TB and HIV epidemics.

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Clinical meningitis (headache, neck stiffness, multiple cranial palsies, confusion) in TB-endemic, HIV-prevalent, resource-poor environment

Focal signs

No

Yes

CT scan (hydrocephalus, basal enhancement/infection)

CRX positive for TB

CSF (≥ 1-week history)

Lymphocytosis ≥ 200 cells/μL

Hypoglycorrhachia ≥ 2.2 mmol/L

CSF-blood glucose ≤ 0.2

Protein ≥ 0.5 g/L

CLAT neg

Gram neg

HIV pos, CD4 ≤ 200 cells/μL

Rapid Tests

Microscopy: 6 mL CSF, 3,000 gravity for 20 min.

200 μL on slide over 1 cm2, examine for 30 min.

PCR (if available)

LAM ≥ 0.18 (OD)

IFN-Υ ≥ 0.224 IU/L

ELISPOT ≥ 46 SFU

All 3 Neg

Consider alternative diagnosis*

If no contraindication:

Mass lesions (toxoplasmosis, lymphoma, tuberculosis, tuberculoc or bacterial abscesses)

Neg

Pos

Treat for TBM

Any test Pos

BY VINOD PATEL, MD

Dr. Patel is in the department of neurology at the University of KwaZulu-Natal, Durban, South Africa.

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Seizure Frequency May Be Key

Epilepsy • from page 1

The rate of definite or probable SUDEP was 0.9 per 1,000 person-years in patients who received efficacious AED doses, 3.7 in those who received non- efficacious doses, and 6.9 in those who received placebo. The incidence of SUDEP in the placebo group was in the highest range of those previously reported in refractory epilepsy and about twice the rate recorded in open-label add-on AED studies, according to the researchers.

The odds of definite or probable SUDEP were significantly lower among patients randomly assigned to AEDs at efficacious doses than they were among and those assigned to placebo (odds ratio, 0.17). The association did not change when possible cases of SUDEP were also considered.

“In our view, the most probable explanation for the very low SUDEP rate recorded in patients allocated to AEDs at efficacious doses during the blinded phase of randomized trials is the treatment-related reduction in seizure frequency,” they wrote.

Patients and caregivers also might take specific precautions during randomized trials, including better compliance or reinforcement, thereby reducing the risk of SUDEP, the researchers suggested.

However, many consider the risk-to-benefit ratio of adjunctive AEDs in refractory epilepsy to be low due to very low rates of long-term seizure freedom, disputable clinical relevance of an incomplete reduction in seizure frequency, and frequent side effects. Previous case-controlled studies also have found that the risk of SUDEP rises with the number of prescribed AEDs, which might make physicians reluctant to prescribe additional AEDs to the baseline regimen of patients with refractory epilepsy even though the association is probably confounded by the relation between the number of AEDs and epilepsy severity, the researchers noted.

“Our data suggest that add-on AEDs at doses effective on seizure frequency reduce the risk of SUDEP despite increasing the drug load, at least during the average 3-month duration of randomized trials,” the researchers wrote. “This finding provides an argument not only for active revision and optimum management of treatment in patients with uncontrolled seizures, but also for further prospective and long-term investigations of this unsettling issue.”

Dr. Ryvlin has received speaker or consultant fees from Pfizer, GlaxoSmithKline, UCBJ Pharma, Eisai, and BIAL. Another author reported receiving speaking fees from Pfizer and UCBJ Pharma.
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BY MARK HALLETT, MD
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Wolters Kluwer/Lippincott Williams & Wilkins, Philadelphia, 2011

Blume's Atlas of Pediatric and Adult Electroencephalography
By WT Blume, GM Holloway, M Kaibara, GB Young
Wolters Kluwer/Lippincott Williams & Wilkins, Philadelphia, 2011

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Electroencephalography (EEG) is a traditional laboratory test for neurology, still useful even after the onslaught of neuroimaging with its pretty pictures, and still read by neurologists. In the United States, all neurologists can read EEGs, but special expertise can be demonstrated by taking the examination in Clinical Neurophysiology by the American Board of Psychiatry and Neurology (ABPN) and/or the examination by the American Board of Clinical Neurophysiology (a freestanding Board). The ABPN certification has to be renewed every 10 years. The two books arrived for review by WORLD NEUROLOGY just as I was studying for my ABPN recertification, and I was happy to see them.

Niedermeyer's book has been the standard comprehensive textbook in the field. With 1,275 pages and 58 chapters, all written by experts in the field, it should contain everything you want to know. This sixth edition of the book certainly contains lots of information, but because each chapter has a different author, the depth of coverage in each area differs by author and there is little continuity from chapter to chapter. It is a book for the expert, not the beginner. It is also not a book you can just pick up and read; it is so heavy, that it has to be kept on the table! Fortunately, the book is also available online after purchase, and I found it easier to read it that way. The book covers a range of topics including evoked potentials, intraoperative monitoring, cognitive function, neuropharmacology, and poly somnography. This is an excellent resource for reading an occasional chapter or looking up a detail and is nice to have on the shelf for anyone wanting to call him or herself an expert.

Blume's Atlas, while a first edition, follows two earlier editions of separate volumes of adult and pediatric EEG. There is nothing that can replace actually seeing and reading a wide variety of EEGs in order to maintain expertise. The book is published with wide pages that look like an EEG page. Each section is preceded by some text. The book is also best left on the table, but that's not unreasonable for reading EEGs, and it is also available online after purchase. The examples are good, clear, and abundant. The book can be read cover to cover and can be used as a ready resource of examples of EEG patterns.

Text on Central Nervous System Tumors
Focuses on a Dynamic Area of Study

Primary Central Nervous System Tumors: Pathogenesis and Therapy
Edited by Andrew D. Norden, David A. Reardon, and Patrick Y.C. Wen
Humana Press, 2010

When judging the value of books, it does well to remember Sir Francis Bacon's comment “…some books are to be read only in parts, others to be read, but not curiously, and some few to be read wholly, and with diligence and attention.” Primary Central Nervous System Tumors fits solidly into the last category in that its intellectual content is as reflective of current knowledge as is possible for any scientific book. I say that because the shelf life of a book such as this could well be relatively short given that it focuses on a rapidly expanding field of knowledge.

The coverage of the topics and the list of contributors are impressive. The book is organized into three sections: General Principles (7 chapters), Gliomas (5 chapters), and Other Tumor Types (10 chapters) and, in general, the chapters are well written and each is highly informative. Some chapters' content (such as the one on ependymomas) has a limited scope because the role of chemotherapy in this disease in adults is yet to be defined.

The chapter on pediatric brain tumors is well written, but a single chapter on the subject in a book that is written primarily for an audience of adult neuro-oncologists does not do justice to the field of pediatric neuro-oncology in which many pioneering clinical trials have been conducted. The book does not address neurological complications of systemic cancer, but that is understandable since it is about CNS tumors.

One shortcoming of the book is its lack of summary tables. In a field such as neuro-oncology, in which much of the new information is gleaned from clinical trials, this book would be more helpful to the reader if the data were organized in table form.

The purpose of writing a book should be as effective as any other teaching activity. It is not enough to present excellent content in a format that does not help the learner retain the information. In the chapter on low grade glioma (LGG), the authors did not make mention of an important fact about the role of gross total resection in a group of patients with low-risk, low-grade glioma (LRLGG). The RTOG 9813 clinical trial, which the authors quote in their chapter, enrolled patients with LRLGG as well as patients with high-risk, low-grade glioma (HRGG). The HRGG patients were randomized to radiation alone vs. radiation plus chemotherapy, and the LRLGG was a no-treatment, observation-only group. In the LRLGG group, the size of residual tumor on the postoperative MRI was highly predictive of the risk for recurrence. These data have been useful in the design of ongoing clinical trials in LGG.
Update on the Neurological Exam Includes Much Information That Is Not Readily Available


This updated sixth edition of DeMyer's classic textbook presents detailed information on how to perform a neurological examination, lavishly illustrated with excellent and clear diagrams and occasional photographs.

The student is first provided with an outline of the standard neurological examination, which is somewhat daunting in its length. As with previous editions, each chapter begins with a discussion of neuroanatomical information relevant to the neurological examination and an understanding of the physical signs.

In fact, it is more than a description of how to examine the neurological system; there is a detailed presentation of the techniques, common abnormalities, and a differential diagnosis of some of the abnormal signs. The text encourages the reader to participate in the learning process with the inclusion of interactive questions to which answers are provided in the margin of the page.

Terms are defined (very useful for those unfamiliar with neurological jargon), and there are clinical examples to illustrate the significance of signs and their localization.

The first six chapters of the book are devoted to the examination of the head and face – including a description of common facial and skull abnormalities – as well as the cranial nerves; and a brief review of clinical neuroanatomy. Examination of the special senses (taste, smell, hearing, and vestibular function), however, are dealt with in Chapter 9 (after the cerebellar system) and, in my view, would better fit in the section on cranial nerves.

Chapters 7, 8, and 10 detail the examination of the somatic motor, cerebellar, and somatosensory systems, respectively.

The chapter on the somatic motor system includes a valuable section on the principles underlying the evaluation of muscle strength; and the chapter on the somatosensory system provides a detailed guide to examining entrapment neuropathies and on the techniques used in examining low back pain and the sciatica syndrome.

The mental status examination (Chapter 11) is laid out in great detail and includes the evaluation of acute and chronic dysfunction, agnosia, apraxia, aphasias, and primitive reflexes.

The neuroanatomical basis of consciousness and the unconscious state (Chapter 12) is comprehensively detailed and supplemented with lavish illustrations. Chapter 12 also addresses the evaluation of the locked-in syndrome, the persistent vegetative state, and – of great value – how to interrogate the patient presenting with a seizure disorder and syncope.

The pathology of breathing and the localization of brainstem symptoms and signs are also discussed.

Chapter 13 deals with ancillary investigations, including lumbar puncture, CSF abnormalities, currettage, and magnetic resonance spectroscopy. The penultimate chapter (14) focuses on the examination and physical signs relating to conversion disorders and malingering, and the features of nonepileptic seizures are also presented. The book ends with a synopsis of the neurological examination and a formulation of the neurological diagnosis.

This textbook will continue to fulfill the requirements and expectations of students and trainees in neurology. It provides more than a description of the tools and techniques that are pertinent to undertaking a neurological examination.

Some may feel that there is too much information and may find the lengthy text overwhelming, but the authors did not intend the book as a quick crash course on how to perform a neurological examination. Rather, it is a substantial text and a source of much information that is not provided in many other texts on the neurological examination.

Evidence-Based Management of Stroke Edited by José Biller, MD and José A. Ferro, MD, PhD Tfm Publishing Ltd., Shrewsbury, UK, 2011

In recent decades, the outlook for patients with or at risk for a stroke have improved significantly because of the development and use of new pharmacological, surgical, and endovascular interventions, and neurologists' growing understanding of the risks, benefits, and indications of those interventions. We have also identified some interventions that might seem intuitively sensible, such as using stents for patients with intracranial stenosis or dual antiplatelet therapy for patients with small subcortical strokes, but that are in fact harmful.

Clinicians who care for stroke patients have to identify and appraise an ever-expanding pool of clinical trials and epidemiological studies. This is a daunting task, and there is a great need for concise, comprehensive textbooks that summarize what is known about stroke management, identify gaps in knowledge, and are accessible to nonspecialists since most stroke patients worldwide are not treated by vascular neurologists. This new text book edited by José Biller and José Ferro fills that gap.

In its 15 chapters – many by well-known experts in the field – the book covers the gamut of cerebrovascular disease from the treatment of acute ischemic stroke with thrombolytics to the management of intracerebral hemorrhage, subarachnoid hemorrhage, and vascular malformations. The chapters on stroke in children and during pregnancy and the puerperium are particularly valuable, as these topics are often overlooked in short textbooks on stroke.

Most of the chapters are very good and up to date, and some are excellent. I particularly liked the chapters on surgery for stroke, management of unruptured aneurysms and subarachnoid hemorrhage, management of spontaneous intracerebral hemorrhage, cerebral venous thrombosis, management of cerebrovascular complications in cardiac patients, and antithrombotic therapies in stroke prevention because they are clearly written, include all of the relevant literature, and have practical recommendations for care and management.

Although the book was published in Europe, the senior authors of 12 of the 15 chapters are based in the United States, and many of the guidelines and practical issues that are discussed are most relevant to clinical practice in North America. Future editions of the book might do well to include lists of links to resources for readers in other parts of the world and chapters on stroke management in regions with different resources and needs.

The editors begin the book with a table on levels and grades of evidence and had asked the authors to quote levels and grades of evidence for each major point in their respective chapters. For the most part, the authors complied. A table at the end of each chapter summarizes the interventions and the evidence that supports them.

These tables are very helpful because they show what interventions have been tested in randomized trials or large epidemiological studies. They are also illuminating because they show that many of the treatments we currently use are not supported by solid evidence.

One of the pillars of evidence-based medicine is the use of clinical situations as the starting point to search and appraise the literature. This book is eminently practical, but I would like to have read one or two vignettes in each chapter to illustrate how the evidence is applied to specific cases. The book is not a systematic review of the literature (the criteria used to identify papers for each chapter are not listed), the quality of the studies that are used to make recommendations is not appraised, and not all of the available evidence is presented. The chapter on interventions for carotid artery disease and intracranial stenosis, for example, includes a brief discussion of the results of CREST but not the earlier angioplasty and stenting studies. These shortcomings, however, are inevitable with such a short textbook and do not diminish the value clinicians will derive from this volume.

Vascular neurologists will find this book interesting and helpful, though I think it will be particularly valuable for general neurologists and physicians from other specialties who take care of stroke patients.

Dr. Biller and Dr. Ferro have furthered the case for applying rigorously evaluated therapies that are effective and safe to enhance the care of our patients with cerebrovascular disease.
Sleep Disorder Tied to Risk for Dementia, Parkinson’s

By Jeff Evanse

Urgent Intervention After TIA Reduces Stroke Risk

By Jeffrey S. Eisenber

Mild cognitive impairment or Parkinson’s disease developed in 34% of patients with probable REM sleep behavior disorder during nearly 4 years of follow-up in a longitudinal, population-based cohort study. Patients with the sleep disorder had a 2.2-fold greater risk for mild cognitive impairment (MCI) or Parkinson’s disease (PD) than did those without, which is in line with three previous studies of risk for neurodegenerative syndromes in patients referred to sleep or movement disorder clinics, according to Dr. Brendon P. Boot and his colleagues at Mayo Clinic locations in Rochester, Minn., and Jacksonville, Fla. These studies estimated that the rate of parkinsonism or dementia in patients with REM sleep behavior disorder (RBD) varies from 18% to 65%.

The researchers analyzed data from 44 participants with probable RBD and 607 without probable RBD who had agreed to participate in the Mayo Clinic Study of Aging after they had been randomly selected from the population of Olmsted County, Minnesota (Ann. Neurol. 2011 Oct. 31:100.1002/ana.22655).

Unlikely the previous three studies, participants with probable RBD in the current study developed MCI “far more frequently than a movement disorder.” Overall, 14 developed MCI and only 1 developed PD, compared with 90 with MCI and 4 with PD among individuals without probable RBD (1% vs. 60%). The higher risk for MCI or PD associated with probable RBD in the study was not substantially altered after adjusting for obstructive sleep apnea symptoms (which can mimic the symptoms of RBD), after including individuals who withdrew from the study, or after excluding two people with probable RBD who had antidepressant-associated RBD.

Diagnoses of probable RBD were based a bed partner’s responses to the Mayo Sleep Questionnaire, which is a validated screening test with 100% sensitivity and 95% specificity for polysomnography-confirmed RBD.

The study involved patients with at least one follow-up visit (with a median follow-up period of 46 months). The patients had a median duration of probable RBD symptoms of 7.5 years, and the median time from the onset of these symptoms to diagnosis of MCI or PD was 20.7 years.

Earlier studies did not rigorously assess all patients for possible MCI. They found higher rates of Parkinson’s disease, dementia with Lewy bodies, Alzheimer’s disease, or multiple systems atrophy in patients with polysomnography-confirmed RBD. Only one of the three previous studies included MCI diagnoses.

The investigators suspected that the MCI/ PD pattern that they observed in the study may be at risk for developing neurodegenerative syndromes. They found an increased risk of MCI and PD, although this was much more dramatic for MCI. No patients developed dementia, but this is not surprising because patients were free of MCI at baseline. To develop dementia, a patient would have to develop new MCI and then develop dementia in only 4 years. Obviously, the main disadvantage of a population-based study in this context is the absence of polysomnographic confirmation of diagnosis. However, the authors have done their best to deal with the potential confounding. It is important to realize that the inability to confirm the diagnosis on polysomnography would likely underestimate disease risk because the ‘probable-RBD’ group would contain a substantial proportion of people without RBD, who are not at increased risk. It will of course be important to continue to follow this cohort, because the true risk of degenerative disease will become apparent after only longer follow-up periods.

Robert Wood Johnson Foundation, and the Robert H. and Clarice Smith and Abigail Van Buren Alzheimer’s Disease Research Program. Several of the researchers reported receiving support for clinical trials sponsored by Cephalon, Allon Pharmaceuticals, Baxter Healthcare, Elan Pharmaceuticals, and/or Forest Pharmaceuticals. Several also serve as consultants for Elan, Jansen, Eli, and/or GE Healthcare.

Urgent intervention after transient ischemic attack (TIA) as a treatment for acute ischemic stroke can increase a patient’s risk of ischemic stroke at 3 years by more than 30% within the first 3 months after the attack. Studies have shown that urgent intervention can substantially reduce this risk, but little is known about the risk reduction over time. The current study involved patients referred to the hospital between 2 days and 7.5 years after the call for acute care. The TIA team, 12.5 days after the call for attention, and 17.5 days after the call for TIA team follow-up.

Urgent intervention after TIA resulted in a significantly lower cumulative stroke risk than what was predicted with ABCD² criteria after both 7 days (1.6% vs. 4.5%) and 90 days (2% vs. 7.5%).

The study was supported by the Danish Heart Foundation and the Research Council in the former Aarhus County. The authors had no disclosures to report.
Shaul Feldman (1923-2011)

BY ODED ABRAMSKY, MD, PHD

Shaul Feldman was born in Odessa, the Ukraine, in 1923. His father was a neuropsychiatrist and leader in the Zionist movement, and the family immigrated to Palestine-Eretz Israel in 1934. The home atmosphere instilled in him a devotion to Israel and set him on the outstanding path he took in neurology.

In 1943, Prof. Feldman graduated from Herzliah High School in Tel Aviv. He studied medicine at the University of Geneva from 1946 to 1948, when he returned to Israel and served in the medical corps of the Israel Defense Forces during the War of Independence.

He resumed his medical studies in Jerusalem in 1949, graduating with honors in 1952 from the first graduating class of the Hebrew University-Hadassah Medical School. The school had been established by the Hadassah Women’s Organization (HWO) in the United States and the Hebrew University of Jerusalem (HUJI) in 1946, a year after the creation of the State of Israel. The HWO was founded in 1912 in New York to alleviate disease in Palestine. In 1918, the organization opened the Rothshild Hadassah Hospital in Jerusalem. HUJI was founded in 1925 by a group of visionary Americans from Europe and the United States, including Albert Einstein, Otto Warburg, Chaim Weizmann, Sigmund Freud, and Martin Buber. After 1933, many physicians and scientists fled Europe for Jerusalem, where they continued their clinical practice and academic research at Hadassah and at the university. But it was only in 1949 that the HWO and HUJI established the Hebrew University-Hadassah Medical School (HUHMS), which included the Hadassah University Hospital (HUH).

After graduating, Prof. Feldman completed his residency in neurology at the Hadassah University Hospital and became a lecturer in neurology in 1957. He was committed to clinical and academic excellence. He and some of his colleagues from the first classes of HUHMS believed that research and science should be integrated into clinical service and that excellent academic medicine was a condition for excellent clinical medicine.

From 1957 to 1959, Prof. Feldman did postgraduate training in basic and clinical neurosciences. He spent the first year studying experimental neurophysiology and neuroendocrinology at the University of California, Los Angeles with Richard Williams, Horace Magoun, and the second studying clinical neurophysiology and neurology at Mount Sinai Medical School in New York with Irving Wagman and Morris Bender. Back in Jerusalem, he established the neurophysiology laboratory in the department of neurology. It was the first step in turning the traditional clinical department into an academic department.

From 1969, Prof. Feldman was professor and chair of the neurology department at Hadassah University Hospital for 2 decades. He led the department in developing a strong clinical neuroscience orientation, making it the leading department in Israel and renowned worldwide.

Prof. Feldman doted on his students. They are among many of the leading physicians, trained in Jerusalem, who have brought about great advances in academic neurology in Israel and globally. He was proud to have been the first neurology resident accepted by Prof. Feldman when he became department chair. Prof. Feldman was elected chairman of the Israel Neuropsychiatric Association. The combination of neurology and psychiatry was a continuation of the clinical-academic orientation that Central European clinicians and scientists had introduced when they moved to Israel before World War II. Prof. Feldman represented the American approach to scientific medicine and succeeded in establishing by 1971 a new academic neurological association, separate from the psychiatric discipline. Today, the Israeli Neurological Society has several hundred members.

Prof. Feldman also contributed in a monumental way to the advancement of the medical practice in Israel. During his tenure as chairman of the Scientific Council of the Israel Medical Association from 1970 to 1977, he established a national system of board certification examinations at the end of residency. In so doing, the level of practice in all specialties and disciplines in medicine improved significantly throughout Israel. As dean of the faculty of medicine at the Hebrew University from 1977–1981, Prof. Feldman established the BS Med degree for medical students, and by so doing raised the academic requirements of the students at the medical school. He was also instrumental in setting up academic frameworks for the schools of nursing, occupational therapy, and community health within the medical faculty.

For more than 40 years, Prof. Feldman conducted research in the neurophysiology and neuroendocrinology of the limbic system, which plays an important role in autonomic, endocrine, and behavioral mechanisms. He studied the electrophysiological connections of the limbic system and the effects of adrenocortical hormones on its electrical activity, and the role of neural pathways and neurotransmitters in the activation of the hypothalamic-pituitary-adrenocortical axis in response to neural stimuli. His studies showed that the responses to stressful stimuli are not a uniform phenomena but that different stressors involve different neural pathways.

He showed that hypothalamic implants of adrenocortical hormones inhibited the response of the hypothalamic-pituitary-adrenocortical axis to different stressful stimuli and that extra-hypothalamic limbic structures modify the neuroendocrine responses as well as the effects of the negative feedback of the adrenocortical hormones at the hypothalamic level.

His studies contributed to our understanding of the role of neural and hormonal mechanisms in response to stressful stimuli, which are essential for the preservation of life. He contributed enormously to the elucidation of relations between the physiology of the brain and the functioning of the nervous system.

Because of Prof. Feldman’s personal and public achievements and his devotion and contribution to neurological research, he attained national and international status and was elected to key positions in global neurology organizations and received many important awards. He was first President of the World Federation of Neurology; member of the executive committee of the European Federation of Medical Deans; the Israeli delegate to the Councils of the International Brain Research Organization and to the scientific Medical Council of the European Science Foundation. Prof. Feldman was honorary member of the American Neurological Association and the European Neurological Society; fellow by Distinction of the Israel Medical Association; and Israel Prize Laureate in medical research (2005).

Prof. Feldman was a superb clinician and teacher and researcher and brilliant intellectual with a phenomenal memory and depth of knowledge. He was charismatic and humane, a leader of the highest order, and a kind and loyal friend who did his utmost for his patients, students, and colleagues. His last years were difficult: his beloved wife Aviva suffers from neurodegenerative disease and he was deeply moved by her condition. His sight and his hearing began to fail but he retained all his faculties until his death on Sept. 15, 2011. We shall remember him and achieve his goals, and his drive to advance neurology to the forefront of medical achievements nationally and internationally. We mourn the passing of a dear friend, colleague, teacher, and mentor.

Dr. ABRAMSKY is a professor of neurology and Chairman Emeritus of the department of neurology, Hadassah University Hospital, and Dean Emeritus of the Hebrew University Hadassah Medical School, Jerusalem, Israel.
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