Annual Course
Managing Common Complex Symptomatic Epilepsies: Tumors and Trauma

Symposium Chair:
Joseph I. Sirven, MD
Professor and Chairman
Department of Neurology
Mayo Clinic in Arizona
Phoenix, Arizona

Sunday, December 2, 2012
Convention Center – Ballroom 6C, Upper Level
8:45 am – 5:15 pm
OVERVIEW
Trauma and tumors are inextricably linked to epilepsy. Among people with newly diagnosed epilepsy of known cause, primary brain tumors or brain metastasis, and Traumatic Brain Injury (TBI) predominate. Chronic seizures are often the most cited problematic complication to either of these conditions. Both trauma and tumors are complicated by their heterogenous epileptogenic injuries and the spectrum of comorbid conditions. Primary care and specialty physicians alike — including oncologists, neurologists, epileptologists, emergency room physicians — all struggle with how to best manage epilepsy as it pertains to both trauma and tumors as numerous therapeutic strategies are available.

This year’s Annual Course will delve into tumor-based and posttraumatic epilepsy, two of the most common yet challenging symptomatic epilepsies faced on a daily basis, through a multidisciplinary approach. The course is divided into two sessions with the morning session devoted to tumor-based epilepsy and the afternoon to posttraumatic epilepsy. Each session will be framed by common clinical scenarios including adults and children and will be used to discuss how disparate mechanisms lead to epilepsy, how the conditions are diagnosed, the questionable role for antiepileptogenic management and how to best manage the conditions from both a medical and surgical vantage point. The goal of the course is to highlight clinical management while illuminating basic science and practice gaps. Each session will end with a summary and offer a potential algorithm for clinical management for epilepsy related to each condition.

LEARNER OUTCOMES
- Utilize algorithms that describe how best to manage patients with epilepsy related to brain tumors including novel intraoperative monitoring techniques
- Use an evidence-based algorithm for management of the patient with posttraumatic epilepsy
- Perform risk analyses in making treatment decisions regarding prophylactic use of AED in patients with CNS tumors
- Manage patients with metastatic brain tumors with treatment options based on evidence-based best practice.

TARGET AUDIENCE
Basic: Those new to epilepsy treatment or whose background is limited, e.g., students, residents, general physicians, general neurologists and neurosurgeons, other professionals in epilepsy care, administrators.

Intermediate: Epilepsy fellows, epileptologists, epilepsy neurosurgeons “mid-level” providers with experience in epilepsy care (e.g., advanced practice nurses, nurses, physician assistants), neuropsychologists, psychiatrists, basic and translational researchers.

Advanced: Symposium will address highly technical or complex topics (e.g., neurophysiology, advanced imaging techniques, advanced treatment modalities, including surgery)

AGENDA
8:55 am Introduction Overview
Joseph Sirven, M.D.

1. Tumors
8:55 a.m. Case Presentation: Benign Tumor Based Epilepsy
Lily Wong Kisiel, M.D.

9:00 a.m. Epidemiology and Semiology of Tumor Based Epilepsy
Charles J. Vecht, M.D.
9:25 a.m. Panel Flash Session: Tumor Based Factors – Genetic Factors, Tumor Types, Peritumoral Morphological Changes
   Lara E. Jehi, M.D., Steve S. Chung, M.D., Joon Uhm,

9:40 a.m. Prevention of Epilepsy in Tumors? (Insights from Basic Science, glutamate receptors)
   Joon Uhm

10:05 a.m. Break

10:20 a.m. Case Presentation: Refractory Epilepsy Related to Tumor Based Epilepsy
   Jeffrey M. Politsky, M.D.

10:25 a.m. Surgical Issues in Managing Tumor Based Epilepsy: Resection Extent Outcomes/ Timing of Surgery
   Edward Chang, M.D.

10:50 a.m. Intraoperative Monitoring: Role in Epilepsy Based Tumor Surgery (Novel techniques)
   Aatif M. Husain, M.D.

11:15 a.m. Case Presentation: Epilepsy Related to a Malignant Based Tumor
   William O. Tatum, IV, D.O.

11:20 a.m. Debate: Valproic Acid: Drug
   Pro: Ideal Drug in Tumor based Epilepsy Due to Antineoplastic Properties
   Charles J. Vecht, M.D.
   Con: Poor Choice of Drug Due to Adverse Effects and Teratogenic Potential
   Kimford J. Meador, M.D.

11:50 a.m. Morning Summary- Algorithm and Treatment Summary
   Jorge G. Burneo, M.D.

Noon – 2:00 p.m. Lunch Break

2. Trauma
2:00 p.m. Case Presentation: Epilepsy Presenting from Recent Civilian Trauma
   Katherine Noe, M.D., Ph.D.

2:05 p.m. Panel Flash Session: Epidemiology and Risk Factors for Traumatic Epilepsy
   Dale C. Hesdorffer, M.D., Susan T. Herman, M.D., Samuel Wiebe, M.D.

2:25 p.m. Epileptogenesis and Treatment
   Jerome Engel, Jr., M.D., Ph.D.

2:40 p.m. Case Presentation: Epilepsy from a Military Experience
   Sara Schrader, M.D.

2: 45 p.m. Epilepsy from the Military Perspective
   Karen L. Parko, M.D.

3:10 p.m. Debate: Does AED Prophylaxis Work in Post Traumatic Epilepsy
   Marc A. Dichter, M.D., Ph.D. and Patrick Kwan, M.D., Ph.D.
3:40 p.m. Break

3:55 p.m. Case Presentation: Refractory Epilepsy from Trauma
        Eric Kossoff, M.D.

4:00 p.m. Imaging and EEG and Posttraumatic Epilepsy
        Michael R. Sperling, M.D.

4:25 p.m. Nonepileptic Seizures and Trauma
        Martin Salinsky, M.D.

4:40 p.m. Surgical Management of Epilepsy: Complexities-Adhesions, Multiple Foci,
        Encephalomalacia
        Jeffrey P. Blount, M.D.

5:00 p.m. Conclusion: Algorithm and Treatment Summary
        Joseph I. Sirven, M.D.

ACCREDITATION
The American Epilepsy Society is accredited by the Accreditation Council for Continuing Medical
Education (ACCME) to provide continuing medical education for physicians.

CREDIT DESIGNATION
The American Epilepsy Society designates this educational activity for a maximum of 6.0 AMA PRA
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participation in the activity.

ACKNOWLEDGEMENT
This program is supported in part by an educational grant from UCB, Inc. and Novartis
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Nurses may claim up to 6.0 contact hours for this session.

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a provider of continuing pharmacy education.
This knowledge-based activity provides up to 6.0 contact hours. Following attendance, completion of the activity evaluation and verification of attendance, participants will be provided an electronic statement of credit.

ACPE Universal Activity Number (UAN) is 0052-9999-12-2322-L04-P and provides 6.0 contact hours.

International Credits: The American Medical Association has determined that non-U.S. licensed physicians who participate in this CME activity are eligible for *AMA PRA Category 1 Credit™*.

ABPN Core Competencies
The American Board of Psychiatry and Neurology has reviewed the Annual Course and has approved this program as part of a comprehensive lifelong learning program, which is mandated by the ABMS as a necessary component of maintenance of certification.

Core Competencies: Medical Knowledge, System-Based Practice, and Practice-Based Learning and Improvement

FACULTY/PLANNER DISCLOSURES
It is the policy of the AES to make disclosures of financial relationships of faculty, planners and staff involved in the development of educational content transparent to learners. All faculty participating in continuing medical education activities are expected to disclose to the program audience (1) any real or apparent conflict(s) of interest related to the content of their presentation and (2) discussions of unlabeled or unapproved uses of drugs or medical devices. AES carefully reviews reported conflicts of interest (COI) and resolves those conflicts by having an independent reviewer from the Council on Education validate the content of all presentations for fair balance, scientific objectivity, and the absence of commercial bias. The American Epilepsy Society adheres to the ACCME’s Essential Areas and Elements regarding industry support of continuing medical education; disclosure by faculty of commercial relationships, if any, and discussions of unlabeled or unapproved uses will be made.

FACULTY / PLANNER BIO AND DISCLOSURES
**Joseph Sirven, M.D. (Chair)**
Dr. Joseph Sirven (Joe) is a Professor of Neurology and Chairman of the Department of Neurology at the Mayo Clinic in Arizona. He is currently Education chair for the Epilepsy Section of the American Academy of Neurology, Chair of the Annual Course Committee for the American Epilepsy Society and Chair of the Professional Advisory Board for the Epilepsy Foundation. In 2011, he served on the Institute of Medicine committee on the Epilepsies. He is editor-in-chief of Epilepsy.com. He has authored numerous publications in several journals and books. He is editor of four textbooks in epilepsy.

Dr. Sirven discloses receiving support as Consulting/Advisory Board Activity from Neuropace Eisai UCB; as Research Funding from For Profit Commercial Sources/Principle Investigator from Eisai.

**Jeffrey Blount, M.D.**
Dr. Jeffrey Blount is a Pediatric Neurosurgeon at Children's of Alabama/UAB whose primary academic interest is the surgical treatment of epilepsy in children. Dr. Blount graduated from the University of Rochester School of Medicine in 1989 and completed the Neurosurgery Residency at the University of Minnesota Residency in 1996 (with an infolded fellowship in epilepsy surgery with the MINEP group /Dr. Robert Maxwell). He completed a fellowship in Pediatric Neurosurgery at the Hospital for Sick Children in 2000 where he worked with Drs. James Rutka, Carter Snead and Hiroshi Otsubo. He is currently the Surgical Director of the Pediatric Epilepsy Surgery Program at Children's of Alabama.

Dr. Blount has nothing to disclose.
Jorge Burneo, M.D., M.S.P.H.
Associate Professor of Neurology, Biostatistics and Epidemiology, Western University, London, Canada, and Co-Director of the Epilepsy Program. A graduate from Universidad Peruana Cayetano Heredia in Lima, Peru, he completed his residency at the Henry Ford Health System, and epilepsy fellowship at the University of Alabama at Birmingham, were he also obtained a Masters of Science in Public Health, with specialty in Epidemiology. He is currently the Director of the EEG Laboratory at the London Health Sciences Center and Co-Leader of the Epilepsy Discovery Project, a research initiative recently funded by the Ontario Brain Institute.

Dr. Burneo, M.D., M.S.P.H. discloses receiving support as Speakers Bureau Member (supported by for-profit entities) from UCB Canada; as Consulting/Advisory Board Activity from UCB Canada; as Research Funding from For Profit Commercial Sources/Principle Investigator from UCB Canada.

Edward Chang, M.D.
Dr. Edward Chang is Associate Professor of Neurological Surgery at UC San Francisco. His clinical expertise is surgical treatment for intractable epilepsy and brain tumors. He specializes in neurophysiologic brain mapping methods, including awake speech and motor mapping, to safely perform neurosurgical procedures in eloquent areas of the brain. He is the recipient of the NIH Director’s New Innovator Award, Klingenstein Fellowship, and Grass Foundation Young Investigator Award. Dr. Chang directs a clinical research program that focuses on outcomes, decision-making, and safety improvement of surgical treatment options for epilepsy.

Dr. Chang has nothing to disclose.

Steve Chung, M.D.
Dr. Chung is a professor of neurology and epileptologist at the Barrow Neurological Institute in Phoenix. He is also director of clinical epilepsy research and epilepsy monitoring unit at the same institution. Dr. Chung burned his medical degree at the Northwestern University school of medicine in Chicago, Illinois. After graduating, he completed his residency in neurology at UCSF. His fellowship in clinical electrophysiology and epilepsy were also conducted at UCSF. He had received many teaching awards and has been principal investigator for clinical epilepsy research.

Dr. Chung discloses receiving support as Speakers Bureau Member (supported by for-profit entities) from GSK, Lundbeck, UCB pharma; as Consulting/Advisory Board Activity from Easi, Lundbeck, UCB Pharma, Upsher-Smith; as Research Funding from For Profit Commercial Sources/Principle Investigator from Esai, GSK, Lundbeck, Medtronix, Neuronex, SK life, Supernus, Sunovion, UCB, Upsher-Smith, UCB.

Marc Dichter, M.D., Ph.D.
Marc Dichter, M.D., Ph.D. is Professor of Neurology and Pharmacology at the University of Pennsylvania, Director of the Mahoney Institute of Neuroscience, and former Director of the Penn Epilepsy Center. Dr. Dichter is active as a clinician, clinical researcher, basic researcher, and educator. His research involves both basic neuroscience and clinical investigations, focusing on mechanisms underlying seizures, actions of AEDs, and epileptogenesis. His research also involves translational and clinical studies in new approaches to treating intractable epilepsy and methods for preventing epilepsy. Dr. Dichter is a past president of the AES.

Dr. Dichter has nothing to disclose.
Jerome Engel, M.D., Ph.D.
Jerome Engel, Jr., MD, PhD, is Director of the Seizure Disorder Center, and The Jonathan Sinay Distinguished Professor of Neurology, Neurobiology, and Psychiatry and Biobehavioral Sciences at UCLA. He is past president of the ACNS, the AES, and the ILAE, and is past co-chair of the Global Campaign against Epilepsy. His bibliography lists over 1,000 publications and over 30 books, and he is principal investigator on three research grants from the NINDS. He has received numerous awards and honors, including a Fulbright Scholarship, a Guggenheim Fellowship, and a Javits Award.

Dr. Engel has nothing to disclose.

Susan Herman, M.D.
Dr. Susan Herman is an Assistant Professor of Neurology at Harvard Medical School and an attending neurologist at Beth Israel Deaconess Medical Center. Dr. Herman received her undergraduate degree from Johns Hopkins University and her medical degree from Columbia University College of Physicians and Surgeons. She completed an internship in internal medicine, residency in neurology, and fellowship in epilepsy and clinical neurophysiology at Columbia-Presbyterian Medical Center in New York. Her clinical research focuses on treatment of refractory epilepsy and continuous EEG monitoring and seizures in critically ill patients.

Dr. Herman discloses receiving support as Research Funding from For Profit Commercial Sources/Principle Investigator from Lundbeck, local PI. UCB Pharma, local PI.

Dale Hesdorffer, Ph.D.
Dale Hesdorffer, Associate Professor in the Sergievsky Center at Columbia University, serves on several editorial boards, the professional advisory board of the Epilepsy Foundation of America, the American Epilepsy Society Task Force on psychiatric aspects of epilepsy, and the American Academy of Neurology SUDEP guidelines workgroup. She was a member of the Institute of Medicine Committee on the Public Health Dimensions of the Epilepsies and the IOM Committee on Gulf War and Health: Long-Term Consequences of Traumatic Brain Injury. Her work on the epidemiology of epilepsy covers many risk factors for developing epilepsy.

Dr. Hesdorffer discloses receiving support as Consulting/Advisory Board Activity from Mount Sinai Injury Prevention Center, UCB Pharma, UpsherSmith, Esai.

Aatif Husain, M.D.
Dr. Husain completed Neurology residency at the Medical College of Pennsylvania and fellowships in clinical neurophysiology, sleep medicine, and EMG at Duke University Medical Center. Currently he is Professor of Medicine in the division of Neurology and Director of the Neurodiagnostic Center, Durham, VAMC.

Dr. Husain discloses receiving support as Speakers Bureau Member (supported by for-profit entities) from UCB Pharma, Jazz Pharma; as Consulting/Advisory Board Activity from UCB Pharma, Jazz Pharma, USL Pharma; as Intellectual Property Ownership from Demos Medical Publishing.

Lara Jehi, M.D.
Dr Lara Jehi is an adult epileptologist at the Cleveland Clinic Epilepsy Center where she serves as the head of the Outcomes Research Program, and the Director of Research. She also serves as the Associate Program Director of the Clinical Research Unit at Cleveland Clinic within the auspices of the Clinical and Translational Science Collaborative. She is board certified in Neurology and Psychiatry, and Clinical Neurophysiology. She has authored several peer-reviewed original manuscripts, editorials and book chapters addressing various aspects of epilepsy surgery outcomes research.
Dr. Jehi has nothing to disclose.

**Eric Kossoff, M.D.**
Dr. Kossoff is an Associate Professor of Neurology and Pediatrics at Johns Hopkins University School of Medicine in Baltimore, Maryland. He completed his Pediatrics training at Eastern Virginia Medical School followed by Child Neurology and Clinical Neurophysiology at Johns Hopkins. He is an expert on the use of nonpharmacologic treatments for children with epilepsy, specifically dietary treatments such as the ketogenic and modified Atkins diet. Dr. Kossoff also has specific interests in infantile spasms, hemispherectomy, Doose syndrome, and Sturge-Weber syndrome.

Dr. Kossoff discloses receiving support as Consulting/Advisory Board Activity from Atkins Nutritionals, Eisai, Nutricia; as Research Funding from For Profit Commercial Sources/Principle Investigator from Nutricia.

**Patrick Kwan, M.D., Ph.D.**
Dr. Kwan is Professor of Neurology at the University of Melbourne, Royal Melbourne Hospital, Australia, and Associate Consultant at the Prince of Wales Hospital, Hong Kong. He has published widely on the outcomes of epilepsy and pharmacology of antiepileptic drugs. His other research interests include the mechanisms of drug resistance, personalised medicine, and genetics of epilepsy. He serves on the editorial boards of a number of epilepsy journals. He is currently President of the Hong Kong Epilepsy Society, treasurer of the ILAE Commission on Therapeutic Strategies, and chaired the task force for the definition of drug-resistant epilepsy.

Dr. Kwan discloses receiving support as Speakers Bureau Member (supported by for-profit entities) from GSK, UCB Pharma; as Consulting/Advisory Board Activity from GSK, Eisai; as Research Funding from For Profit Commercial Sources/Principle Investigator from Eisai, UCB Pharma.

**Kimford Meador, M.D.**
Dr. Meador is Professor of Neurology and Pediatrics at Emory University, and Director of epilepsy and Director of Clinical Neuroscience Research. He is a behavioral neurologist and epileptologist. Dr. Meador has authored over 300 peer reviewed publications. His research interests include: pharmacology and physiology of cognition, and epilepsy with focus on behavioral and cognitive co-morbidities and the impact of therapies. He is PI of a multicenter investigation on pregnancy outcomes in women with epilepsy including neurodevelopmental effects of antiepileptic drugs.

Dr. Meador discloses receiving support as Consulting/Advisory Board Activity from the Epilepsy Study Consortium that receives money from multiple pharmaceutical companies; Dr. Meador has consulted in this regard for NeuroPace, Norvartis, UCB Pharma, Upsher Smith Laboratories, and Vivus Pharmaceuticals. Note that funds for consulting for the Epilepsy Study Consortium are paid to Emory University; as Research Funding from For Profit Commercial Sources/Principle Investigator from In last 5 years, Dr. Meador has received research funding from Cyberonics, GlaxoSmithKline, Eisai, Marius, Myriad, Neuropace, Pfizer, SAM Technology, Schwartz Biosciences, UCB Pharma.

**Katherine Noe, M.D., Ph.D.**
Katherine Noe is an adult epileptologist practicing at the Mayo Clinic in Arizona, where she is an Assistant Professor of Neurology. Dr. Noe completed her neurology training at Baylor College of Medicine. Fellowship training in EEG and epilepsy followed at Mayo Clinic in Rochester, Minnesota.

Dr. Noe discloses receiving support as Research Funding from For Profit Commercial Sources/Principle Investigator from NeuroPace, Inc.- institutional research funding.

**Karen Parko, M.D.**
Karen L. Parko, MD, is the National Director of the Veterans Affairs Epilepsy Centers of Excellence and a professor of neurology at the University of California at San Francisco. Dr. Parko retired from the U.S. Public Health Service after serving 24 years of active duty as a commissioned officer. She is a fellow of the American Academy of Neurology and a member of the American Epilepsy Society. She is active in the Epilepsy Foundation of America and serves on the Professional Advisory Board of the National Organization and previously chaired the Professional Advisory Board of the Northern California Chapter. Dr. Parko has nothing to disclose.

Jeffrey Politsky, M.D., FRCP(C)
Degrees: BSc (Neuroscience, Psychology) & MSc (Pharmacology) – Univ of Toronto; MD: Univ of Western Ontario, London, ON Neurology Residency: Univ of BC, Vancouver, BC 2-Yr Epilepsy Fellowship: Harvard/MGH, Boston, MA
Current Positions: Assoc Director & Research Co-Director, Northeast Regional Epilepsy Group; Medical Director, MEG & Functional Brain Mapping Center and Atlantic Neuroscience Inst Epilepsy Program, Overlook Medical Ctr, Summit, NJ. Current Academic Titles: Clinical Assoc Prof (Neurology), Mt Sinai School of Medicine, NY, NY; Primary Interests: Tumor-Related Epilepsy, ICU Monitoring, Functional Brain Mapping.

Dr. Politsky has nothing to disclose.

Martin Salinsky, M.D.
Dr. Salinsky is Professor of Neurology at the Oregon Health & Sciences University, and director of the Portland VA Epilepsy Center of Excellence, in Portland, Oregon. His primary research interests include the cognitive and EEG effects of antiepileptic drug therapy, and clinical and psychological aspects of psychogenic non-epileptic seizures. He is currently involved in ongoing studies of traumatic brain injuries and seizures in US veterans.

Dr. Salinsky discloses receiving support as Speakers Bureau Member (supported by for-profit entities) from UCB, Inc.

Sara Schrader, M.D.
Dr. Sara Schrader, MD, completed her neurology residency and fellowship in Clinical Neurophysiology at Mayo Clinic in Arizona. She went on to serve active duty in the Air Force at Wilford Hall Medical Center and Brooke Army Medical Center in San Antonio, TX from 2009-2012. She is currently practicing with JWM Neurology in Indianapolis, IN.

Dr. Schrader has nothing to disclose.

Michael Sperling, M.D.
Dr. Sperling is Baldwin Keyes Professor of Neurology at Thomas Jefferson University in Philadelphia and Director of the Jefferson Comprehensive Epilepsy Center. He has published extensively in the fields of epilepsy and clinical neurophysiology and lectures throughout the U.S. and internationally. He is well known for his studies of epilepsy surgery outcome, intracranial EEG, and pharmacological therapy of epilepsy. He is past president of the American Clinical Neurophysiology Society, the Philadelphia Neurological Society, and is an active member of the AES.

Dr. Sperling discloses receiving support as Consulting/Advisory Board Activity for research study design: Sunovion, Upsher-Smith; as Research Funding from For Profit Commercial Sources/Principal Investigator from Sunovion, Eisai, UCB Pharma, SK Life Sciences, Vertex Pharm., Medtronics, Neuronex.
William Tatum, D.O.
Dr. William Tatum is Professor of Neurology in the Mayo College of Medicine. He is the director of the Epilepsy Monitoring Unit at Mayo Clinic in Florida. He is a fellow in the American Academy of Neurology with qualifications in neurophysiology, president-elect of the American Board of Clinical Neurophysiology, fellow, council member, and Annual Course chairman in the American Clinical Neurophysiology Society. He has authored or co-authored over 90 peer-reviewed articles, 20 book chapter, and 2 books on epilepsy and neurophysiology. His research interests include drug-resistant epilepsy, EEG, and clinical neurophysiology.

Dr. Tatum has nothing to disclose.

Joon Uhm, M.D., FRCPC
Joon Uhm is a staff neurologist in the Department of Neurology at Mayo Clinic with a cross appointment to the Department of Medical Oncology. He obtained his medical degree from McGill University in Montreal, Canada, and completed residency in Neurology at the Montreal Neurological Institute and McGill University. Following fellowship training in Neuro-Oncology at MD Anderson Cancer Center in Houston, TX, he joined the Mayo Clinic staff where his primary responsibilities are for the care of brain tumor patients.

Dr. Uhm has nothing to disclose.

Charles Vecht, M.D., Ph.D.
Charles J. Vecht MD PhD (1947) is a neurologist and founder of Neuro-oncology Dept. at the Rotterdam Cancer Center, and former chairman of the Brain Tumour Group of the EORTC in Bruxelles, Belgium. Since 2000 he is at the Dept. Neurology, Medical Centre The Hague, both as chairman and in charge of the Neurology Residency Program. He has authored >160 peer-reviewed papers on Neuro-oncology or Epilepsy and sits on the board of a number of medical journals. From 2012, he continues to work in Paris (Neuro-oncology Dept, CHU Pitié-Salpêtrière) and in Heemstede, The Netherlands (SEIN Foundation of Comprehensive Epilepsy Clinics).

Dr. Vecht discloses receiving support as Consulting/Advisory Board Activity from Consultancy fees from UCB Pharma; as Research Funding from For Profit Commercial Sources/Principle Investigator from Research grants from UCB Pharma, Eisai and GlaxoSmithKline.

Samuel Wiebe, M.D.
Samuel Wiebe is Professor and Head of Neurology, Deputy Chair of the Department of Clinical Neurosciences, and Associate Dean of Clinical Research at the University of Calgary in Canada. He is Director of the Neurosciences Clinical Research Unit in the Hotchkiss Brain Institute in Calgary, Canada. His areas of academic interest include surgical trials in epilepsy, epidemiological studies, outcome assessment, and health services research. Dr Wiebe is past-chair of the North American Regional Commission of the International League Against Epilepsy and is currently Secretary-General of the International League Against Epilepsy.

Dr. Wiebe has nothing to disclose.

Lily Wong-Kisiel, M.D.
Lily Wong-Kisiel is an assistant professor in neurology at the Mayo Clinic Rochester. She completed her child neurology residency, fellowship in clinical neurophysiology, and fellowship in pediatric epilepsy at the Mayo Clinic. She is involved in the pediatric epilepsy surgery program at there. Her primary research interests are in the presurgical evaluations for medically refractory epilepsy.

Dr. Wong-Kisiel has nothing to disclose.
**Paul Levisohn (Medical Content Specialist)**
Dr. Levisohn is Associate Professor of Pediatrics and Neurology at the University of Colorado School of Medicine and Children’s Hospital Colorado. He is former medical director of the Epilepsy Monitoring Unit at The Children's Hospital. He has served as chair of the AES Practice Committee, is co-chair of the advisory committee for the National Center for Project Access at the Epilepsy Foundation and is a member of the EF Professional Advisory Board. He currently serves as consultant to AES on medical content of AES continuing medical education activities.

Dr. Levisohn has nothing to disclose.

**Dave Clarke, (Liaison Reviewer)**
Dr. Dave Clarke received his medical degree at the University of the West Indies. He completed his residency at Overlook Hospital, an affiliate of Columbia University College of Physicians and Surgeons, and received his Pediatric Neurology training at the University of Michigan Medical Center, and Neurophysiology (Epilepsy and Sleep) at the Hospital for Sick Children, University of Toronto, in Toronto, Canada. Dr. Clarke is currently Director of the Comprehensive Epilepsy Program at Dell Children’s Medical Center of Central Texas in Austin, TX.

Dr. Clarke discloses receiving support as Speakers Bureau Member (supported by for-profit entities) from ONFI (Sabril) and Cyberonics.

**Anne Comi, MD (Liaison Reviewer)**
Dr. Anne Comi is an Associate Professor in Neurology and Pediatrics at the Kennedy Krieger Institute and Johns Hopkins School of Medicine. She directs the Hunter Nelson Sturge-Weber Center there. She leads a clinical consortium of centers, within the NIH funded Brain Vascular Malformation Consortium, with the goals of developing a national de-identified database and novel biomarkers for Sturge-Weber syndrome and determining the cause of SWS. She oversees NIH funded translational laboratory research dealing with ischemia and seizures and the impact of pharmacologic and cellular interventions upon regeneration in the immature brain.

Dr. Comi has nothing to disclose.

**Kevin Haas, MD (Liaison Reviewer)**
Dr. Haas is an adult neurologist and epilepsy specialist at Vanderbilt University. He has board certification in neurology, clinical neurophysiology, and epilepsy monitoring and am the director of epilepsy surgery at Vanderbilt. His research interests include epilepsy in neurodevelopmental diseases, pharmacogenomics of antiepileptic medications, surgical treatments for epilepsy, and diagnosis and management of status epilepticus. His basic research experience has focused on GABA-A receptor physiology, synaptic roles of ubiquitination, and epilepsy in Angelman syndrome.

Dr. Haas discloses receiving support as Research Funding from For Profit Commercial Sources/Principal Investigator from UCB - PI for drug study Neuronex - PI for drug study.

**Bassel Shnecker, MD (Liaison Reviewer)**
Dr. Shnecker is an epileptologist at Ohio State University. He is an Associate Professor and Vice Chair in the Department of Neurology.

Dr. Shnecker discloses receiving support as Research Funding from For Profit Commercial Sources/Principal Investigator from Clinical trials: UCB, GSK, Eisai, Upsher-smith, Vertex; as Research Funding from For Profit Commercial Sources/Principal Investigator from UCB, Eisai, Sanovian (CLinical trials).
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Opinions expressed with regard to unapproved uses of products are solely those of the faculty and are not endorsed by the American Epilepsy Society or any manufacturers of pharmaceuticals.

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The Medical Education Evaluator® is an online system allows any attendee to self-manage the process of completing course evaluations, tracking credits and printing out the appropriate certificate for either AMA PRA Category 1 Credits™, CE or ACPE pharmacy statement of credits.

Log on to the Evaluator via the AES website at www.aesnet.org. Once you are on the Evaluator, you will be asked to enter your MyAES ID # and password. The certificate(s) are saved to your personal account page which is cumulative. You may print the certificate(s) in PDF format at any time.

To help support this process, AES members who want CME will be asked to pay $35 before January 18 and $50 between January 19 and February 28. Non-AES attendees who want CME will be asked to pay $50 before January 18 and $75 between January 19 and February 28.

The online Evaluator will be left open through February 28, 2013. You must complete the evaluations and credit tracking by that date.

By completing this information online, attendees greatly assist the Council on Education and Annual Meeting Committee with important needs assessment data whereby the AES can further plan and address educational gaps to meet the needs of our learners.

A meeting attendance certificate will be available for international meeting attendees at the registration desk.

SYLLABUS
Syllabi for the educational symposia are available to print in the AES Virtual Tote Bag. Paper handouts will not be provided on site.
Annual Course: Managing Common Complex Symptomatic Epilepsies: Tumors and Trauma
December 2, 2012
Joseph I. Sirven, MD
Professor and Chairman
Department of Neurology
Mayo Clinic Arizona
Phoenix, Arizona USA

Annual Course Overview
• Trauma and Tumors are linked to epilepsy.
• Both TBI and brain tumors are overrepresented in newly diagnosed patients
• Chronic seizures are the most cited problematic complication to either of these conditions
• Models for learning and preventing epileptogenesis

Annual Course: Learning Objectives
• Utilize Algorithms that describe how to best manage patients with epilepsy related to brain tumors including novel intraoperative monitoring techniques
• Use an evidence based algorithm for management of the patient with posttraumatic epilepsy
• Risk Analyses will be performed in making treatment decisions regarding prophylactic use of AEDs in patients with CNS tumors
• Manage Patients with metastatic brain tumors with treatment options based on evidence-based best practices

Disclosure
Eisai, MAP, Vertex, Research Grants
Upsher-Smith, Lundbeck, UCB, Neuropace, NIH
Benign Tumor Case Presentation
December 4, 2012

Lily Wong-Kisiel, MD
Assistant Professor in Neurology
Child and Adolescent Neurology, Pediatric Epilepsy
Mayo Clinic
Rochester, MN

16 Year-old Right Handed Female

• No seizure risk factor
• Single seizure semiology since age 11 years
  – Increased heart rate or sensation of intense anxiety
  – Stereotypic complex visual black / white hallucinations
    • Little people dancing around a giant
    • Herself sitting on a rock
  – Preserved speech
  – 30 seconds

Seizure Recurrence

• Age 13 Years
  – Off medication for 4 months before recurrence
  – Same semiology
  – MRI brain showed ‘right temporal cortical dysplasia’
• Ages 14-16 years
  – Weekly seizures despite additional medication trials
  – Neuropsychometric testing
    • Verbal memory intact
    • Verbal / nonverbal skills normal

Disclosure

None

Age 11 years

• MRI brain showed right ‘mesial temporal sclerosis’
• Short-term EEG repeatedly normal
• Prolonged video EEG
  – Single event of “funny feeling /panic sensation”
  – Two to 3-Hz delta activity at T4 for ten seconds
• Management
  – Carbamazepine and topiramate
  – Seizure free for 2 years

Age 11 years

T1 with gadolinium

FLAIR

Age 13 years

T1 with gadolinium

FLAIR

Faint gadolinium enhancement in the anteromedial right temporal lobe
16 Year-old Right Handed Female

Intervention

- Right temporal lobectomy and amygdalohippocampectomy
- Pathology:
  - Angiocentric glioma WHO Grade I
- Gross total resection on follow-up MRI
- Medication withdrawal at 3 month
- Seizure free off medication at 15 months
Epidemiology and Semiology of Tumor-based Epilepsy

Charles J. Vecht
Medical Center The Hague
SEIN Epilepsy Foundation, The Netherlands
CHU Pitié-Salpêtrière, Paris, France

Disclosure of Conflicts of Interest

Charles Vecht MD PhD
has received Consultancy fees from UCB Pharma;
Research Grants from UCB Pharma, Eisai and
GlaxoSmithKline; Travel Funding from UCB Pharma.

Published Papers on Epilepsy & Brain Tumors

<table>
<thead>
<tr>
<th></th>
<th>&gt; 1992 - ‘12</th>
<th>&gt; 2002 -’12</th>
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</thead>
<tbody>
<tr>
<td>Epilepsy</td>
<td>80,967</td>
<td>49,822</td>
</tr>
<tr>
<td>+ 20,1 %</td>
<td>+ 38,4 %</td>
<td></td>
</tr>
<tr>
<td>Cancer</td>
<td>1,682,914</td>
<td>1,066,927</td>
</tr>
<tr>
<td>+ 20,7 %</td>
<td>+ 36,6 %</td>
<td></td>
</tr>
<tr>
<td>Brain Tumors</td>
<td>93,450</td>
<td>57,032</td>
</tr>
<tr>
<td>+ 20,9 %</td>
<td>+ 39,0 %</td>
<td></td>
</tr>
<tr>
<td>Epilepsy &amp; Br.Tumors</td>
<td>3,048</td>
<td>1,888</td>
</tr>
<tr>
<td>+ 17,2 %</td>
<td>+ 38,0 %</td>
<td></td>
</tr>
<tr>
<td>Epilepsy &amp; AEDs</td>
<td>21,427</td>
<td>13,025</td>
</tr>
<tr>
<td>+ 21,1 %</td>
<td>+ 39,2 %</td>
<td></td>
</tr>
</tbody>
</table>

Epilepsy in Brain Tumours
Epidemiology & Semiology

- Type of Seizures
- Type of Tumor
- Localization of Tumor
- Hereditary Tumors
- Systemic Cancer
- Diagnostic Issues
- Prognostic Factors

Epilepsy in Brain Tumours
Mechanisms

- Underlying Mechanisms
- Genetic Factors
- Molecular Biology
- Peri-Tumoral Changes
- Treatment-Resistance
Epilepsy in Brain Tumours

Treatment

- Medical Management
  - Prophylaxis of Seizures & Peri-operative Period
  - Seizure Control with AEDs
  - Drug-Drug Interactions
- Anti-Tumor Therapy
  - Surgery
  - Radiation Therapy & Systemic Chemotherapy
  - Interaction of AEDs with Tumor Control
- Toxicity Issues
  - Side-Effects
  - Quality of Life / Cognitive Changes

In General Population with New Onset Epilepsy

- Overall Frequency of Brain Tumors is 4 %
- Over 25 years of age 15 %
- Surgery for Intractable Epilepsy 12 - 25 %

In Brain Tumors:
- Frequency of Epilepsy is > 40 %
- In Low-grade Brain Tumors
  Frequency of Epilepsy > 75 %

Epilepsy in Systemic Cancer

- In > 4 %
- Metabolic Encephalopathies
  - Organ Dysfunction
- Toxic Encephalopathies
  - Iatrogenic
  - Antibiotics, Interferons
  - Systemic Chemotherapy
  - Antidepressant & Neuroleptic Agents
- Often of Cumulative Nature (Co-Morbidities)
- Opportunistic CNS Infections
- Radionecrosis

Underlying Mechanisms

- Imbalance Adjacent Cortical Inhib. / Excit. Mechanisms
- Tumour Type: Developmental Tumors associ. with Cortical Dysplasia and Well-diff. Cells, Time-course
- Aberrant Neuronal Migration, Synaptic Vesicles Glutamate, Glutamate-Decarboxylase, Gaba-Receptor
- Changes in Micro-environment:
  - Angiogenesis, Perfusion, Hypoxia, pH
- Hypoxia: Lower Stability of DNA-Repair, Mutations
- Secondary Epileptogenesis: Temporal Location & Time Course

Seizure Frequency in Brain Tumours

Disturbed Small Networks

[Image: Magnetic resonance imaging (MRI) showing a left temporal tumor (astrocytoma III). (B) Synchronization likelihood (SL) graph at a threshold of 0.15 (0.5–60Hz) obtained from the means of SL values in the whole control subject population. (C) SL graph (same parameters) from Patient BER. (D) Regions (dashed areas) showing an increase in MCPs in comparison with control subjects (Z-score > 1.96). Bartolomei & Stam, 2006]
Disturbed Small-World Network

Patterns of connectivity loss in the gamma band in three patients (14, 10, and 2). Synchronization likelihood (SL) graphs were built at a threshold of 0.05 in the gamma band (30-60 Hz). In the last column, the regions (dashed areas) showing a decrease in missing connective points in comparison with control subjects (Z-score 1.96) are indicated.

Bartolomei & Stam, 2006

Initializing of Abnormal Circuits Inducing Seizures in Brain Tumors

- Disruption of Neuronal Connections with Inhibition of Local Network Regulation
- Impaired Glial Cell Activity
- Increased Vascular Permeability and Abnormal Blood-Brain-Barrier
- Deregulation of Adjacent Brain Areas with Peritumoral Edema and Inflammation, Necrosis, Hemosiderin Deposition

Proportion of Drug-Resistant Epilepsies

Etiological factors and AED resistance

- Pre-perinatal damage
- Low-grade glioma/NET
- Vascular accident
- MTS
- Cortical malformations
- CNS infection
- Head trauma
- Vascular malformation
- Other causes
- Other brain malformations
- Chromosomal/gene
- Plasminogen

Proportion of Drug-Resistant Epilepsies

H.W. Mesdag, 1890

Beach of Scheveningen

Proportion of Drug-Resistant Epilepsies

Gilioli 2012

Proportion of Drug-Resistant Epilepsies

Calatozollo 2012
Association between MDR Protein Expression and Treatment-Response

Drug Interactions between Anti-Epileptic Drugs (AEDs) and Chemotherapeutic Drugs (CTDs)

Major CYP-450 Enzymes

First-Generation Antiepileptic Drugs

Effect of Enzyme-Inducing AEDs on Pharmacokinetics of Chemotherapeutic Drugs

- Carbamazepine >95% hepatic Inducer
- Phenobarbital 75% hepatic, 25% renal Inducer
- Phenytoin >90% hepatic Inducer
- Valproate >95% hepatic Inhibitor

CYP 3A4 50%
CYP 2D6 25%
CYP 2C9 15%
CYP 2C19 5%

Patsalos & Perucca 2003

Brodie et al, 2012
Survival of Children with B-lineage Leukaemia

**Probability of CCR**

![Graph showing survival rates](image)

**Number at risk**

- No anticonvulsants: 476 450 365 285 221 157 68 0
- Anticonvulsants: 14 17 14 14 14 14 14 0

Relling 2000

---

P450 Drug-Drug Interactions Websites:

- [http://medicine.iupui.edu/clinpharm/ddis/](http://medicine.iupui.edu/clinpharm/ddis/)

---

**Prophylactic AEDs Trials in Brain Tumors**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Tumor Type</th>
<th>AED</th>
<th>Placebo</th>
<th>OR (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Forsyth</td>
<td>Metastatic Glioma</td>
<td>PHT</td>
<td>11/46</td>
<td>15/54</td>
</tr>
<tr>
<td>Glantz</td>
<td>Metastatic Glioma</td>
<td>VPA</td>
<td>13/37</td>
<td>9/37</td>
</tr>
<tr>
<td>Francesetti</td>
<td>Metastatic Glioma</td>
<td>PHT</td>
<td>3/41</td>
<td>4/22</td>
</tr>
<tr>
<td>North</td>
<td>Metastatic Glioma</td>
<td>PHB</td>
<td>9/42</td>
<td>5/39</td>
</tr>
</tbody>
</table>

---

**Type of Low-Grade Tumors**

- **144 (70%)** Classic Epilepsy-Associated Tumours
  - 82 Ganglioglioma
  - 29 Dysembryoblastic Neuroepithelial Tumour
  - 33 Pilocytic Astrocytoma
  - 5 Pleomorphic Xanthoastrocytoma

- **59 (27%)** Other Tumours
  - 38 Astrocytomas gr II
  - 17 Oligodendrogliomas gr II

- **4 (2%)** Grade III tumours
  - 3 Astrocytoma gr III
  - 1 Ganglioglioma gr III

Luyken 2003
Seizure Semiology in Low-Grade Glioma

- Secondary Generalized Sz. 67.1%
- Simple Partial 23.7%
- Complex Partial 6.6%
- Partial & Sec. Generalized 2.6%
- Single Pre-operative Sz. 34.3%

You 2012

Seizure Semiology in Glioblastoma Multiforme

- As Presenting Sign: 123 (42.1%)
- Seizures: 181 (62%)
- Secondary Generalized: 74 (40.8%)
- Simple Partial: 59 (32.6%)
- Combined Partial & Sec. Generalized: 26 (14.4%)
- Complex Partial: 9 (5%)

De Wit - Kerkhof, 2012

Seizure Characteristics in Low-Grade Glioma (n = 508)

- Mean Age 38.1 yrs
- 45 % Astrocytomas, 9 % Oligodendrogliomas, 46 % Oligo-Astrocytomas (LGG)
- Cortical Location 31 %, Subcortical 69 %
- Frontal 71 %, Temporal 37 %, Insular 21 %, Parietal 9 %
- Pre-op Seizures 68.9 %
- Med. Duration of Sz. Onset and Surgery 10 Mos

You 2012

Standard Treatment in Glioblastoma Multiforme (GBM)

Chemoradiation with Temozolomide particularly effective with methylated MGMT

Effect of Radiation Therapy and of Systemic Chemotherapy

EORTC Study on Radiotherapy in LGG

- Seizure-Freedom with Early RT: 75 % (n = 314)
- Late RT: 59 %

- Temozolomide in Low-grade Gliomas
- TMZ Cohort n = 39; Control group n = 30
- Median length of F-U: 39 vs. 37 Months
- > 50 % Decrease in Sz frequency
  With TMZ: 59 %; Control group: 13 % (p < .001)

Van den Bent 2006; Sherman, 2011
Recommendations
Refractory Epilepsy

• Consider Surgery
  (rather than Wait & See)

• Consider Radiotherapy & Chemotherapy

Brain Tumor and Epilepsy: Effect of Tumor Type
December 2, 2012
Lara Jehi, MD
Cleveland Clinic

Learning Objectives
• Summarize most essential facts relating tumor type to the clinical manifestations of epilepsy.
• Summarize the most critical implications of tumor type on epilepsy treatment.

Fact 1:
Tumor type is one of the main determinants of the risk of epilepsy [Park, 2010]

Fact 2:
Timing of seizures in relation to diagnosis- rather than tumor type- determines seizure characteristics [Klawans, 2004]

Table 2.2: Seizure frequency in various brain tumor types

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Seizure Frequency (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dysembryoplastic neuroepithelial</td>
<td>100</td>
</tr>
<tr>
<td>tumor (DNT)</td>
<td></td>
</tr>
<tr>
<td>Ganglioglioma (G)</td>
<td>10-90</td>
</tr>
<tr>
<td>Low-grade astrocytoma (L)</td>
<td>10</td>
</tr>
<tr>
<td>Medulloblastoma (M)</td>
<td>10-40</td>
</tr>
<tr>
<td>Glioblastoma multiforme (GBM)</td>
<td>20-30</td>
</tr>
<tr>
<td>Pilocytic CNS lymphoma (PLC)</td>
<td>10-20</td>
</tr>
</tbody>
</table>

Disclosure
None
Fact 3:
Tumor type is one of the main determinants of the risk of associated epileptic pathology

**Dual Pathology**

- Developmental brain tumors: DNET and gangliogliomas
- Malformation of cortical development (Frater, 2000; Morris, 1996; Jehi, 2008)
- Hippocampal sclerosis (Prayson, 2008)

What is behind the “facts”?

**Tumor type:** (Jehi, 2008)

- Necrosis
- Endothelial proliferation
- Mitosis
- Tissue infiltration

Low grade

High grade

Fact 1:
Tumor type is one of the main determinants of the risk of epilepsy (Jehi, 2008)

**Determinants of excitability**

Mechanisms of Epilepsy!
Fact 1:
Tumor type is one of the main determinants of the risk of epilepsy (Jehi, 2010)

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Low grade</th>
<th>High grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diffuse astrocytoma (DA)</td>
<td>100%</td>
<td>75%</td>
</tr>
<tr>
<td>Glioblastoma (GB)</td>
<td>80-90%</td>
<td>80-90%</td>
</tr>
<tr>
<td>Low-grade astrocytoma (LG)</td>
<td>75%</td>
<td>75%</td>
</tr>
</tbody>
</table>

Timing of seizures in relation to diagnosis - rather than tumor type - determines seizure characteristics (Hildebrand, 2005)

<table>
<thead>
<tr>
<th>Tumor Type</th>
<th>Low grade</th>
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</tr>
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<td>Low-grade astrocytoma (LG)</td>
<td>75%</td>
<td>75%</td>
</tr>
</tbody>
</table>

Association with hippocampal sclerosis
Consideration particularly with long standing epilepsy

Association with MCD

American Epilepsy Society | Annual Meeting 2012

Fact 2:
Tumor type is one of the main determinants of the risk of associated epileptic pathology

Dual Pathology

Developmental brain tumors: DNET and gangliogliomas

25%-70% Malformation of cortical development (Frater, 2000; Morris, 1996; Jehi, 2008)

Hippocampal sclerosis (Prayson, 2008)

American Epilepsy Society | Annual Meeting 2012
Fact 4:

• In general, risk of developing intractability is at least 50% when tumor is the etiology.
• Twice as high as the risk of intractability with other causes of epilepsy.

Impact on Clinical Care and Practice

• Recognize high risk of seizures in all patients with brain tumors.
• Recognize that adequate epilepsy control requires adequate treatment of the tumor.
• Consider early surgery
• Tumor surgery is NOT the same as epilepsy surgery.

Thank you!
Peritumoral Changes and Epileptogenesis

December 2, 2012

Steve Chung, MD
Professor of Neurology
Barrow Neurological Institute

American Epilepsy Society | Annual Meeting

Learning Objectives

• What causes seizures in brain tumor patients?
• Understand the various peritumoral changes that contribute to seizures

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Does size, grade, or location matter?

• High-grade gliomas are less often associated with seizures (30-40%), and smaller tumors are more likely present with seizures
• Low grade glioneuronal tumors (i.e. gangliogliomas and DNETs) are more often associated with seizures (80-100%)
• Seizures are more likely to occur if tumors are in mesial temporal and insular structures

Are tumor-related seizures due to peritumoral changes rather than the tumor itself?

1 Lee JH: Arch Neurol. 2010; 67(1)
2 Prayson RA: Ann J Surg Pathol 2010; 34

Are seizures caused by the tumor or peritumoral tissue?

• Intrinsic epileptogenicity of brain tumors is supported by the presence of hyperexcitable neuronal components within the tumor
  • i.e. Dysplastic neurons and giant cells of cortical tubers
  (Alteration of glutamate and GABA receptor expressions)
• Also, the dysplastic and disorganized peritumoral region may cause epileptogenesis via Distorsion and Infiltration.

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Changes in peritumoral tissue

by high-grade tumors

• Rapid growth causes tissue damage (Distortion)
  • Necrosis
  • Hemosiderin deposition
  • Peritumoral edema
• High-grade tumors present less frequently with seizures
  • i.e. in GBM, 30-50%

1 Perrier et al. Epilepsia. 2006

American Epilepsy Society | Annual Meeting 2012

Disclosure

Received research grants: Barrow foundation, Esai, GSK, Lundbeck, Medtronics, Neuronex, SK Life Science, Spernum, Sunovion, UCB Pharma, Upsher-Smith, Valeant

Member of speaker’s bureau: GSK, Lundbeck, UCB Pharma

Consulting/Advisory Board: Esai, Lundbeck, UCB Pharma, Upsher-Smith

Upsher-Smith Consulting/Advisory Board: Esai, Lundbeck, UCB Pharma
Member of speaker’s bureau: GSK, Lundbeck, UCB Pharma
Sunovion, UCB Pharma, Upsher-Smith

11/14/2012
Changes in peritumoral tissue  
Initial thoughts

- Penfield in 1940: Seizures are due to impaired vascularization and peritumoral ischemic changes
- Echlin in 1959 proposed partial isolation or denervation hypersensitivity theory

Changes in peritumoral tissue  
Altered living environment (1)

- Ion changes may cause hyperexcitability
- Decreased extracellular Mg
- Increased extracellular Fe
- pH changes may cause hyperexcitability
- Peritumoral cortex is significantly alkaline
- Altered carbonic acid levels
- Alkalinity blocks membrane K⁺ conductance
- pH increase causes reduced GABA levels and activates NMDA receptors

Changes in peritumoral tissue  
Altered living environment (2)

- Changes in amino acid concentration
  - Inhibition of glutamate transporters (GLAST, GLT1, EAAC1) → extra cellular glutamate level increase
  - Altered GABA level and GABAergic transmission
  - Increased level of polyamines (Spermine, spermidine, putrescine)
  - Enzymatic changes (e.g. Glutamine synthetase)

These changes may be a cause or a consequence of seizures

Changes in peritumoral tissue  
Altered living environment (3): IL-1β

- Immune mediated changes occur in peritumoral region
- Elevated IL-1β level in brain tumor
  - Elevated IL-1β in acute/chronic seizure models
  - Proconvulsive effects of IL-1β
    - Augments nitric oxide formation
    - Directly inhibits GABA
    - Increases NMDA receptor function
    - Inhibits K⁺ efflux

Changes in peritumoral tissue  
Altered living environment (4): TNFα, BBB

- Up-regulation of TNFα mRNA after seizures and in subjects with CNS tumors (in animal)
- TNFα may play a dichotomous role
  - Activates p55: proconvulsant effect
  - Activates p75: anticonvulsant effect
- Cytokines cause enhanced BBB permeability
Summary: Peritumoral tissue and Epileptogenesis

- Aberrant neuronal/glial neosynapses
- Disturbed balance of excitatory/inhibitory inputs
- Membrane instability and altered neurotransmitter concentrations
- Cytokine/TNF mediated membrane excitability
- Disruption of the blood-brain-barrier
Panel Flash Session: Tumor-based Factors: Genetic Factors, Tumor Types, Peritumoral

Joon Uhm, MD

Slides not available
Prevention of Epilepsy in Tumors: Insights from Basic Science, Glutamate Receptors

Joon Uhm, MD

Slides not available
Tumor-Related Epilepsy: Case Presentation

Sunday, December 2, 2012

Jeffrey M. Politsky, MD, MSc, FRCP(C)
NORTHEAST REGIONAL EPILEPSY GROUP
Medical Director, MEG & Comprehensive Epilepsy Center
Atlantic Neuroscience Institute, Summit, NJ
Clin Assoc Professor of Neurology, Mt Sinai School of Medicine, NY

Learning Objectives

- Mechanism of tumor-induced epilepsy
- Influence of epileptic network on tumor growth
- Impact of treatment on epileptogenesis and tumorigenesis
- Standardizing treatment approach
  - Pharmacologic & Alternative Therapies
  - Surgical therapy

Case 1

65 yo female with a 1-yr hx of recurrent episodes c/b sudden onset of a feeling of dread, associated with blurred vision and feeling faint, lasting 1-2 mins
Freq: Crescendo characteristic - daily
ERF: negative
PM/S Hx: MCTD, cardiac dysrhythmia, LASIK
Soc Hx: comp programmer, divorced, one child, no tob/eth/IDU
Neuro Exam: elemental exam intact

Disclosure

Name of Commercial Interest  |  Type of Financial Relationship
--- | ---
- Nothing to Disclose  |  Nothing to Disclose
Case 1

- **Diagnosis:**
  - 1.2 Brain, right craniotomy for tumor resection
  - Meningioma, grade I (WHO 2007).

- nearly one-year post-op
- No sz
- On AED monotherapy
- Focal slowing on EEG
- **Prognosis:** good
  - QOL considerations: Duration of therapy? Tumor recurrence.

Case 2

- 43 year old male
- Presented in May 2011 with a 30 sec episode of R facial twitching and speech arrest
- Several brief (5 s) episodes in prior months discounted by patient
- Epilepsy Risk Factors: none
- PM/S Hx: sinusitis, benign vocal cord polyp
- Soc Hx: Wall St Broker, 15 pk yr hx cig; intermittent binge drinker; int THC use
- Neuro Exam: R facial droop
Case 2

**Diagnosis:**
- Brain, left temporal lobe craniotomy for biopsy of mass:
  - Glioblastoma multiforme, grade IV, (WHO 2007)
- Comments:
  - Proliferation of small astrocytic cells, appearing as "naked" nuclei in a fibrillary background;
  - Hyperchromatic nuclei - round to spindled, coarse chromatin and rare nucleoli;
  - Vascular proliferation with endothelial hyperplasia and mitotic figures;
  - Cellular proliferation strongly positive for GFAP
  - scantly nuclear reactivity for p53 and an 80% labeling index for p67;
  - Extensive tumoral calcifications in some areas;
  - usually associated with oligodendroglial tumors, but in this case overall cytomorphologic and histologic features are more compatible with GBM.

**Tumor-Related Epilepsy**
- Mechanism of tumor-induced epilepsy
  - Intra-axial tumors (gliomas, metastatic lesions)
  - Extra-axial tumors (atypical meningioma)
- Influence of epileptic network on tumor growth
- Impact of Tx on epileptogenesis/tumorigenesis
- Standardizing treatment
  - Pharmacologic & Alternative Therapies
    - Ketogenic/Low Gycemic Index/Modified Atkins Diets
  - Surgical therapy

**Case 2**

- One year post-op
- On AED polypharmacy (3 AEDs) to maintain reasonable control
- Adjuvant Therapy: bevacizumab, temozolomide
- Rt hemiparesis, expressive > receptive aphasia
  - rehab program
- Prognosis: poor
  - QOL considerations: Optimizing Tx, AE, DDI, tumor recurrence, further Tx options, progressive disability, end of life
Surgical Issues in Managing Tumor-Based Epilepsy: Extent Resection Outcomes, and Timing
December 2, 2012
Edward Chang, MD
University of California, San Francisco

Learning Objectives

• To understand the predictors of seizure-freedom in patients with brain tumors
• To understand factors which affect quality-of-life and cognition in patients with tumor-related epilepsy

Disclosure

none

European Journal of Cancer 1998

Table 3. Prevalence of epilepsy in the non-brain tumor subgroup of 1021 intracranial gliomas diagnosed between 1980 and 1995

<table>
<thead>
<tr>
<th>Histology</th>
<th>Epilepsy prevalence*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glioblastoma (n=915)</td>
<td>256 (47%)</td>
</tr>
<tr>
<td>Anaplastic glioma (n=132)</td>
<td>93 (69%)</td>
</tr>
<tr>
<td>Low-grade gliomas (n=379)</td>
<td>302 (86%)</td>
</tr>
</tbody>
</table>

*P<0.001, chi-square.

Epilepsy in Low-Grade Gliomas: The Impact on Cognitive Function and Quality of Life

"The increase in epilepsy burden that was associated with significant reductions in all cognitive domains except for attentional and memory functioning could primarily be attributed to the use of AEDs, whereas the decline in HRQOL could be ascribed to the lack of complete seizure control."
Predictors of Seizure Freedom (Engel Class 1)

<table>
<thead>
<tr>
<th>Predictor</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gross Total Resection</td>
<td>16</td>
<td>2.2-124</td>
</tr>
<tr>
<td>Simple partial seizures</td>
<td>0.36</td>
<td>0.18-0.72</td>
</tr>
<tr>
<td>Seizures &gt;1 year duration</td>
<td>0.28</td>
<td>0.1-0.56</td>
</tr>
</tbody>
</table>

Take-home for LGG-epilepsy

Tumor control:
- GTR → 10 year survival = 100%
- STR → 10 year survival < 50%

Seizure control:
- GTR → seizure freedom = 85%
- STR → seizure freedom < 35%
Intractable epilepsy in paralimbic World Health Organization Grade II gliomas: should the hippocampus be resected when not invaded by the tumor?

Clinical article

ENDLER, M.D., AND BECKETT DUNG, M.D., PH.D., 1,2

N=15
All patients seizure-free with additional hippocampal resection
Also, all returned to work

Conclusions:
Decision-making for tumor-related epilepsy is more straightforward than non-lesional epilepsy surgery

Subtotal vs Gross-total resection is critical for seizure-freedom and long-term survival
Epilepsy surgery approach is more appropriate than tumor approach
- Familiarity with intraop electrocorticography
- Familiarity with mesial temporal structures/anatomy
- Anatomic approach is better
- Consideration of risks: memory/eloquence

Does pathology matter? Not really.
- Outcomes nearly same for LGG/DNET/GG

Controversies:
Timing:
If suspicion of glioma, then operate. Do not wait.
- up to 50% of non-enhancing tumors are anaplastic astrocytomas (worse prognosis, require chemo/radiation)
- GG and DNET can be difficult to distinguish from LGG/AA

Controversies:
Resection- how much to take?

Temporal lobe: lesionectomy vs lobectomy?
Lateral temporal or insular: resect or spare hippocampus?
Extratemporal: lesionectomy vs extended lesionectomy (with intraoperative electrocorticography)?
Is there a role for chronic intracranial monitoring?

Controversies:
Resection- how much to take?

Medial temporal lobe: lesionectomy vs lobectomy?
- If refractory epilepsy → lobectomy

Lateral temporal or insular: resect or spare hippocampus?
- If epilepsy → resect hippocampus

Extratemporal: lesionectomy vs extended lesionectomy (with intraoperative electrocorticography)?
- Extended lesionectomy

Is there a role for chronic intracranial monitoring?
- NO, seizure localization rarely difficult; outcomes are excellent without it

Impact on Clinical Care and Practice
- Text
- Text
Intraoperative Monitoring: Role in Epilepsy Based Tumor Surgery
December 2, 2012

Aatif M. Husain, M.D.
Duke University and Veterans Affairs Medical Centers, Durham, NC

Learning Objectives

• Understand technique and utility of language mapping
• Understand techniques used for motor cortex localization
• Compare various techniques used for motor mapping and monitoring

Overview

• Language mapping and monitoring
• Central sulcus/motor cortex localization
• Motor pathway monitoring
• Intraoperative ECoG

Language Mapping

• Rationale
  – Localization of language areas very variable
  – Resection in “eloquent” area may be possible
  – Identifies clinical function of neural tissue
• Cautions
  – Mapping may result in seizures
  – After discharges must be monitored
  – Awake patient

Language Mapping – Technique

• Cortical areas stimulated with bipolar constant-current stimulator (Penfield technique)
  – 60 Hz trains of biphasic pulses
  – Each pulse 1 ms. (2-10 mA per pulse)
  – Train duration 3 – 5 seconds
• ECoG obtained with strip electrode(s)
• After discharge threshold identified
• Mapping performed with stimulation intensity 2 mA less than AD threshold
• Naming task performed

Disclosures

<table>
<thead>
<tr>
<th>Name of Commercial Interest</th>
<th>Type of Financial Relationship</th>
</tr>
</thead>
<tbody>
<tr>
<td>UCB Pharma</td>
<td>Research, consultation, speaker bureau</td>
</tr>
<tr>
<td>Upsher Smith Laboratories</td>
<td>Research, consultation</td>
</tr>
<tr>
<td>Jazz Pharma</td>
<td>Consultation, speaker bureau</td>
</tr>
<tr>
<td>Demos Medical Publishing</td>
<td>Royalties</td>
</tr>
</tbody>
</table>
Patient 1: 24 year old, right-handed woman started having CPS 6 months prior to referral to epilepsy center. Seizure have continued despite treatment with LEV and LCM.

Patient 1: After Discharge

ARS Question
Should language mapping be performed in all cases of dominant hemisphere fronto-temporal-parietal tumor/epilepsy surgery?

A. Yes
B. No
C. No opinion
Language Monitoring

- Resection rule: resect > 1 cm. from essential site to avoid functional deficit
  - Visual naming task
- Monitor language function during resection
  - Testing during resection
  - Testing with electrical stimulation
- 7 patients with LGG in Broca’s area
  - Resection with language mapping and monitoring
- Stimulation during resection caused language deficits
  - White matter between anterior insula and pars orbitals (anterior margin)
  - Fibers from ventral premotor cortex (posterior margin)
  - Anterior part of arcuate fasciculus (depth)
  - Head of caudate nucleus
- Postoperatively transient language worsening but no permanent deficits

Central Sulcus/Motor Cortex Localization

- Rationale
  - Location of central sulcus not visually obvious, especially in cases of tumors
  - Resection in “eloquent” area may be possible
  - Identifies clinical function of neural tissue
- Cautions
  - Mapping may result in seizures
  - Injury to white matter fiber tracts can cause complications

Patient 2: 15 year old male with ganglioglioma and epilepsy refractory to medications; undergoing tumor resective surgery.

Patient 2: 5 year old male with tuberous sclerosis and multiple cortical tubers with medically refractory epilepsy – undergoing surgery to resect left parietal lesion.

Median SEP Technique

- Stimulation of median nerve
- Recording from exposed cortex with strip/grid electrode
- “Referential recording” with distant reference
- Largest amplitude N20 over somatosensory cortex
- Anterior-posterior phase reversal marks central sulcus
- Electrode position must be moved to check for variations, especially when lesions present
Patient 2:
Central Sulcus Localization – Tibial N.

Electrical Stimulation Technique
- Cortical areas stimulated with bipolar constant-current stimulator (Penfield technique)
- ECoG obtained with strip electrode(s)
- Observation of face/limbs
- EMG monitoring of face/limbs
- After discharges monitored
- Clinical seizures common

ARS Question
I use electrical stimulation (Penfield method) for motor cortex localization during tumor surgery for epilepsy.

A. True
B. False
C. Uncertain

EMG Recording
- EMG recording from face, limbs increased sensitivity of motor mapping
- 24% of patients had clinical or subclinical seizures during mapping
- Mapping method less likely to produce seizures needed

Direct Cortical Stimulation Technique
- Stimulation (anode) with strip electrode placed on cortex; same electrode used for median SEP
- Cathode placed distally
- Monopolar stimulator can be used
- Standard stimulator with 0.5 ms pulse width
- 5 pulse train, 2.1–4 ms ISI
- Stimulation intensity up to 20 mA/60 V
  – Some report intensities up to 25 mA/110 V*
- EMG recording electrodes in face, limbs

Direct Cortical Stimulation

Mapping
- Nonrecurrent pulse trains used
- Subdural strip placed perpendicular to central sulcus
- Various contacts on subdural strip sequentially stimulated
- Hand-held bipolar or monopolar stimulator can be used
- Site of lowest intensity stimulus evoking MEP response is over motor cortex

Monitoring
- Strip electrode rotated to lie parallel to central sulcus
- Lowest stimulus intensity that evokes MEP used
- MEP recorded from restricted group of muscles
- Multiples sites may need to be stimulated to evoke hand/leg responses
- Hand and foot sites stimulated with monopolar or bipolar derivation
- Repeated throughout surgery

Patient 2: 5 year old male with tuberous sclerosis and multiple cortical tubers with medically refractory epilepsy – undergoing surgery to resect left parietal lesion.

Subcortical Mapping with Intraoperative Imaging
- 42 patients with corticospinal tract tractography co-registered to surgical navigation-derived images
- Direct subcortical stimulation with monopolar stimulator, 0.1-25 mA intensity; recording from muscles
- Intraoperative ultrasound during stimulation; compared to tractography based neuronavigation
- Stimulation thresholds compared to distance to corticospinal tracts

Subcortical Mapping - Tractography
- Stimulation threshold increases approximately 1 mA/mm of distance from CST
- Subcortical MEP threshold of 3 mA is cutoff for new CST deficits

ARS Question
Motor cortex mapping and monitoring reduces morbidity.
- True
- False
- Uncertain

Review of Motor Mapping/Monitoring

<table>
<thead>
<tr>
<th>Mapping</th>
<th>Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>No change (n=48)</td>
<td>MEP preserved (n=48)</td>
</tr>
<tr>
<td>Temporary MEP loss (n=12)</td>
<td>4 (41)</td>
</tr>
<tr>
<td>Permanent MEP loss (n=3)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>
- MEP amplitudes vary widely
- Lack of comparable series – uncertain if monitoring reduces morbidity
Conclusions

- Distribution of language sites variable – mapping important to avoid damage
- Motor cortex localization/mapping done with many different techniques
- New mapping techniques have advantages over older methods
- Motor monitoring during tumor dissection may prevent injury to CST
- Utility of motor mapping in reducing morbidity uncertain
Epilepsy Related to a Malignant-Based Tumor

December 2, 2012

William O. Tatum IV, DO, FAAN, FACN
President-elect American Board of Clinical Neurophysiology
Professor of Neurology
Mayo College of Medicine
Senior Consultant, Mayo Clinic and Hospital
Director, Epilepsy Monitoring Unit
Jacksonville, Florida USA

Learning Objectives

• To present a representative case of epilepsy due to a malignant brain tumor.

Malignant Brain Tumor

• Brain MRI later suggested left frontal tumor.
• PFHx: unremarkable for brain tumors but mom did have leukemia and died at 72 years.
• Needle Brain biopsy 11/2007 (University);
  – 15 minute generalized seizure post-operatively.
  – Histology;
    • Oligoastrocytoma (WHO grade 2)
    • FISH testing positive for 1p36 and 19q13 deletion (favorable).

Disclosure

Name of Commercial Interest
None

Type of Financial Relationship
None

Case Presentation

• RW is a 58 year old RHWM was referred by neuro-oncology 4/2010 for uncontrolled seizures.
  • Past history included hypertension, CAD 5/P MI 5/P stenting x 3, hyperlipidemia, & erectile dysfunction.
  • Neurological examination normal 5/2010.
  • In 7/2007 after intermittent chest pain, at 2 am he was found down/confused with a tongue bite.
  • In the ED: CPK was elevated (diagnosed with MI) and CT brain revealed a left frontal “stroke.”
Histopathology

Focal Seizures

• Semiology:
  • "Facial seizures" (every other day):
    • Aura: Subjective sense that eyes are deviating to the right prior to an indescribable feeling x 15-30 seconds.
    • Focal seizure with dyscognitive features and right face/jaw clonic jerking x 2-3 minutes followed by expressive difficulties 15-25 min.
  • "Full-blown seizures" (2 only at onset and after surgery):
    • 1 witnessed in hospital: Speech arrest, loss of consciousness, bilateral symmetrical jerking x 15 minutes with gradual recovery.
  • Frequency: every other day
  • Course: Drug-resistant; progressive

Seizure Semiology

Video

Treatment

• Seizure Treatment
  • Past AEDs: PHT (fatigue), VPA ("sick", nausea, dizzy, sleepy, tremor), PRM (sleepy), LEV (ineffective), OXC (ineffective), LCS (ineffective).
  • Current Medicines: PRT 250 mg po tid, OXC 600 mg po tid; OXP 2.5 mg po qid (Toprol ER 50 mg po qid; ASA 81 mg po qd; Lipitor 40 mg po qd).
  • Brain Tumor Treatment
    • Temozolomide x 20 months (6/2009)
    • High dose XRT to 60 Gy

Clinical Course

• Malignant Brain Tumor (unresponsive to therapy).
• Continued focal seizures despite AEDs.
• Followed locally for ongoing care.

Case Conclusion

• Drug-resistant focal seizures.
• Palliative resective surgery was discussed.
• Neurostimulation was recommended but declined.
• Tumor without response to treatment.
Impact on Clinical Care and Practice

- Brain tumor patients with epilepsy are most concerned with QoL.
- Seizures affect an individual’s threshold for relative disability.
- Side-effects may be more disabling than seizures.

THANKYOU!
Tatum.william@mayo.edu
Valproic Acid: Ideal Drug in Tumor-based Epilepsy due to Antineoplastic Properties

Charles J. Vecht
Medical Center The Hague
SEIN Epilepsy Foundation, The Netherlands
CHU Pitie-Salpetriere, Paris, France

Disclosure of Conflicts of Interest

Charles Vecht MD PhD has received consultancy fees from UCB Pharma; Research grants from UCB Pharma, Eisai, and GlaxoSmithKline; and funding for travel from UCB Pharma.

Which AEDs to use in the Clinical Practice of Neuro-oncology?

Recommended in Brain Tumors

- To Avoid Enzyme-Inducing AEDs
  - i.e. Phenytoin, Carbamazepine, Phenobarbital

- In newly diagnosed Brain Tumors,
  - No Prophylaxis with AEDs

- In newly diagnosed Brain Tumors without Sz,
  - Taper/Discontinue AEDs
  - after 1st Post-operative Week

Choice of AEDs for Partial Epilepsy in Adults

- Different for Brain Tumours?
- Expert Opinion by Karceski et al 2005:

  - LAMOTRIGINE
  - (without co-morbidity)

  - CARBAMAZEPINE
  - (though not in brain tumours)

  - LEVETIRACETAM
  - (with co-morbidity)

Class I Evidence

Dam Square
G.H. Breitner, 1897
Use of AEDS in Glioma Patients

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Total (%)</th>
<th>Postoperative Seizures (%)</th>
<th>Seizures (%)</th>
<th>No. Seizures (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AEDs</td>
<td>480 (94.5)</td>
<td>333 (85.1)</td>
<td>147 (97.0)</td>
<td></td>
</tr>
<tr>
<td>Valproic acid</td>
<td>431 (84.8)</td>
<td>300 (85.7)</td>
<td>131 (82.9)</td>
<td></td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>11 (2.2)</td>
<td>7 (2.0)</td>
<td>4 (2.5)</td>
<td></td>
</tr>
<tr>
<td>Phenytoin</td>
<td>3 (0.6)</td>
<td>1 (0.3)</td>
<td>2 (1.3)</td>
<td></td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>4 (0.8)</td>
<td>1 (0.3)</td>
<td>3 (1.9)</td>
<td></td>
</tr>
<tr>
<td>Combination</td>
<td>31 (6.1)</td>
<td>24 (6.9)</td>
<td>7 (4.4)</td>
<td></td>
</tr>
</tbody>
</table>

| Discont'd % | 19/27 (70.4 %) | 18/35 (51 %) | 15/34 (44 %) |
| Discont'd    | 7/27 (26 %)    | 12/35 (34 %) | 7/34 (20 %)  |

Survival w/o Enzyme-Inducing in GBM and Adjuvant CCNU

<table>
<thead>
<tr>
<th>Treatment</th>
<th>A (# 88) No Seizures</th>
<th>B (# 43) Seizures</th>
<th>C (# 37) Seizures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjuvant CCNU (Lomustine)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CBZ</td>
<td>CBZ (81 %)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VPA</td>
<td>VPA (85 %)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Survival (in months)</td>
<td>11.6</td>
<td>10.8</td>
<td>13.9 p 0.016</td>
</tr>
</tbody>
</table>

Compromised Activity of CTD by Co-Administration of AEDs

<table>
<thead>
<tr>
<th>Cytosphosphamid</th>
<th>PB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ifosfamide</td>
<td>PB</td>
</tr>
<tr>
<td>Thiopeta</td>
<td>PB</td>
</tr>
<tr>
<td>Busulfan</td>
<td>PHT</td>
</tr>
<tr>
<td>Nitrosoureas</td>
<td>PB</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>PHT, CBZ, PB</td>
</tr>
<tr>
<td>Vincaalkaloid</td>
<td>PHT, CBZ, PB</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>PHT, CBZ, PB</td>
</tr>
<tr>
<td>Topotecan</td>
<td>PHT</td>
</tr>
<tr>
<td>Irinotecan</td>
<td>PHT</td>
</tr>
<tr>
<td>Aminocamphotosein</td>
<td>PHT, CBZ, PB</td>
</tr>
<tr>
<td>Temposide</td>
<td>PHT, CBZ, PB</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>PB</td>
</tr>
<tr>
<td>Procarbazine</td>
<td>PB</td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>PB</td>
</tr>
</tbody>
</table>


Autophagy induced by valproic acid is associated with oxidative stress in glioma cell lines

Influence of Valproic Acid on Outcome of High-grade Gliomas in Children

Amejadi Masouedi, Marley Elophe, EJham Amini, Margarete E Nagel, Joann L. Ater, Vidy Gopalakrishnan and Johannes E.A. Wolfg
Valproic Acid =
Histone Deacetylase Inhibitor (HDAC)

Schematic illustration of HDACi mechanism of action. Shown is a schematic illustration of mechanisms by which histone deacetylase inhibitors (HDACi), histone deacetylases (HDAC) and histone acetyltransferases (HAT) modulate gene expression. HATs add acetyl groups to lysine residues of histone tails, contributing to an open and accessible chromatin structure. HDACs remove these groups, resulting in a closed structure, and HDACi reverse this effect.

Valproate

Free Fatty Acid
Broad Spectrum Anticonvulsant
Histone-deacetylase Inhibitor

Prolonged survival with valproate acid use in the EORTC/NCIC temozolomide trial for glioblastoma
Neurology 2011;77:1156; Published online before print August 31, 2011;

Kaplan-Meier Curve of GBM Patients (n = 291) with Chemoradiation by TMZ with and without VPA

Seizure Control in Patients with GBM (n = 291)

Initial Therapy

<table>
<thead>
<tr>
<th>Initial</th>
<th>Seizure-Freedom</th>
</tr>
</thead>
<tbody>
<tr>
<td>VPA</td>
<td>41 / 100 (41.0%)</td>
</tr>
<tr>
<td>LEV</td>
<td>16 / 37 (43.3%)</td>
</tr>
<tr>
<td>VPA + LEV</td>
<td>89 / 116 (76.7%)</td>
</tr>
</tbody>
</table>

Final Treatment

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Seizure-Freedom</th>
</tr>
</thead>
<tbody>
<tr>
<td>VPA Monotherapy</td>
<td>28 / 36 (77.8%)</td>
</tr>
<tr>
<td>LEV Monotherapy</td>
<td>25 / 36 (69.5%)</td>
</tr>
<tr>
<td>VPA + LEV Polyther.</td>
<td>38 / 63 (60.3%)</td>
</tr>
</tbody>
</table>
**VALPROIC ACID**

Advantages

- Broad Spectrum AED
- Longer Survival with VPA vs. CBZ
- Histone-Decetylase Inhibitor

Disadvantages

- Enzyme-Inhibitor
- Thrombopения

Oberndorfer 06; Eyal 06; Class 3 Evidence

---

**Bone-marrow Toxicity of Chemotherapy with Valproic acid**

- Series of 70 Patients with High-Grade Glioma
  - Fotomustine (d3: 100 mg/m2)
  - Cisplatin (d1-3: 33 mg/m2)
  - Etoposide (d1-3: 75 mg/m2)

In Patients on Valproic Acid:
- 3 x more frequent:
  - Grade 3-4 Thrombopenia & Neutropenia

Bourg, Lebrun, Fresay 2001

---

**Haemostatic Risks with Valproic Acid**

N = 87

Preop. Thrombocytes (w, w/o VPA) 235 vs. 277/μL

No Differences for
- Postop. Blood Loss
- RBC Volume
- # Postop. Transfusions

N = 111 with VPA, 202 w/o VPA

Thrombocytes 284 vs. 279/μL

No Differences for
- Postop. Blood Loss
- Postop. Wound Discharge

Anderson 1997, Ward 2004

---

**No Hepatic Metabolism and No Interactions**

- Gabapentin
- Levetiracetam
- Vigabatrin
- Pregabalin
- Lacosamide

---

**Levetiracetam Monotherapy in Brain Tumors**

- > 50% Seizure response: 92 - 95%
- Seizure-Freedom: 63 - 93%

Wagner, 2003; Partap 2008, Maschio 2010, Usery 2010
Choice of AEDs for Partial Epilepsy w/o Sec. Generalisation in Brain Tumors

- VALPROIC ACID*
- LAMOTRIGINE
- TOPIRAMATE
- LEVETIRACETAM* (not registered as monotherapy by FDA in US)

Manson 2000; Privitera 2003; Gamble 2006; Brodie 2007
Class 1, 2 Evidence

Recommendations: Medical Therapy

- Avoid Enzyme-inducing AEDs
- Valproic Acid**
- Levetiracetam*
- Valproic Acid with Levetiracetam*
- Lamotrigine
- Topiramate

** Survival Advantage May Justify Side-effects


Class 2 PREFERENCE

- Valproic Acid (1000 - 3000 mg)
- Levetiracetam (1000 - 4000 mg)
- Combination
  - Valproic Acid (1000 - 1500 mg)
  - Levetiracetam (1000 - 2000 mg)

Bois de Boulogne, Paris
Isaac Israels, 1906

Conclusions

- Better to Avoid Enzyming-Inducing AEDs
- HDACI Activity of Valproic Acid works synergistically with Chemotherapeutic Agents
- Indications that Valproic Acid with Temozolomide prolongs survival in Glioblastoma
- First-line AEDs in Brain Tumors: Valproic Acid or Levetiracetam
  If Seizures continue: VPA and LEV in combination

Karin Boutrus
Hanneke Zwikels
Melissa de Wit-Kerkhof
Janneke Dielemans
Melanie van Breemen
Louis Wagner
Lynn Rijsman
Martin Taphoorn
Erik Wilms
Charles Vecht
Valproate Con: Poor Choice of Drug Use due to Adverse Effects & Teratogenic Potential
December 2, 2012
Kimford Meador, MD
Professor of Neurology & Pediatrics
Emory University
Atlanta, Georgia

Learning Objectives
• To understand our current knowledge of the relative risks of valproate for congenital malformations and poor neurodevelopmental outcomes due to fetal exposures.

• To review other potential adverse effects as they relate to other drug choices.

EUROCAT
European Surveillance of Congenital Anomalies

Case-control study
98,075 cases with malformations among 3.8 million births in Europe
19 registries in 14 countries from 1995 – 2005

Valproate

<table>
<thead>
<tr>
<th></th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spina bifida</td>
<td>12.7 (7.7 – 20.7)</td>
</tr>
<tr>
<td>Atrial septal defect</td>
<td>2.5 (1.4 – 4.4)</td>
</tr>
<tr>
<td>Cleft palate</td>
<td>5.2 (2.8 – 9.9)</td>
</tr>
<tr>
<td>Hypospadias</td>
<td>4.8 (2.9 – 8.1)</td>
</tr>
<tr>
<td>Polydactyly</td>
<td>2.2 (1.0 – 4.5)</td>
</tr>
<tr>
<td>Craniosynostosis</td>
<td>6.8 (1.8 – 18.8)</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>2.6 (1.2 – 5.3)</td>
</tr>
</tbody>
</table>


Disclosures
Grants: GSK, Eisai, Marinus, Myriad, Neuropace, Pfizer, SAW Tech, Schwartz Brosci, & UCB.
NIH/NINDS 2RO1-NS38455. Meador (PI), Neurodevelopmental Effects of Antiepileptic Drugs*
NIH/NINDS U01-NS077366-01. Meador (PI). Emory NEXT Site*
NIH 1RC1DA004863. Thompson (PI). Preventing depression in people with epilepsy.
Epilepsy Foundation of America. Guring (PI). Metabolic and DTA abnormalities in TLE with and without co-morbid depression.
Consultant (note no personal income): Abbott, Cyberonics, Eisai, GSK, Medtronic, Ortho McNeil, Spheres, UCB, & Epilepsy Consortium (funds are paid to Emory U)* for NeuroPace, Neuvatis, UCB Pharma, Upsher Smith & Venus.
Travel: Sanofi-Aventis*
Other: Clinical income: EEG procedures and patient care*
*Items with asterisk involve income > $10,000 for the last year. All industry related income goes to the university or charities.

Meta-analysis: Pregnancy Outcomes in Women with Epilepsy

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Malformations % [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women without epilepsy</td>
<td>3.27 [1.37, 5.17]</td>
</tr>
<tr>
<td><strong>AED Monotherapy</strong></td>
<td></td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>4.62 [3.48, 5.76]</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>2.91 [2.00, 3.82]</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>4.91 [3.22, 6.59]</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>7.36 [3.60, 11.11]</td>
</tr>
<tr>
<td>Valproate</td>
<td>10.73 [8.16, 13.29]</td>
</tr>
</tbody>
</table>


EURAP: Dose Dependent Effects on MCMs

<table>
<thead>
<tr>
<th>Antiepileptic Drug</th>
<th>N</th>
<th>% Seizure Free</th>
<th>% MCMs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;400 mg/d</td>
<td>148</td>
<td>64%</td>
<td>3.4%</td>
</tr>
<tr>
<td>400 to &lt;1000 mg/d</td>
<td>1047</td>
<td>67%</td>
<td>5.3% *</td>
</tr>
<tr>
<td>≥1000 mg/d</td>
<td>207</td>
<td>62%</td>
<td>8.7% *</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;300 mg/d</td>
<td>836</td>
<td>67%</td>
<td>2.0%</td>
</tr>
<tr>
<td>≥300 mg/d</td>
<td>444</td>
<td>68%</td>
<td>4.5% *</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;150 mg/d</td>
<td>166</td>
<td>71%</td>
<td>5.4% *</td>
</tr>
<tr>
<td>≥150 mg/d</td>
<td>51</td>
<td>69%</td>
<td>13.7% *</td>
</tr>
<tr>
<td>Valproate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;700 mg/d</td>
<td>431</td>
<td>71%</td>
<td>5.6% *</td>
</tr>
<tr>
<td>700 to &lt;1500 mg/d</td>
<td>480</td>
<td>66%</td>
<td>10.4% *</td>
</tr>
<tr>
<td>≥1500 mg/d</td>
<td>99</td>
<td>61%</td>
<td>24.2% *</td>
</tr>
</tbody>
</table>

* More MCMs than LT<300mg/d
Tomson et al., Lancet Neurol 2011;10: 609-17
NEAD Age 3 Results: Valproate Group with Lower IQ
Mean IQs (95% CIs difference from VPA) adjusted for maternal IQ, age, AED dose, gestational age & folate:

<table>
<thead>
<tr>
<th></th>
<th>CBZ</th>
<th>LTG</th>
<th>PHT</th>
<th>VPA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean IQ</td>
<td>98</td>
<td>101</td>
<td>99</td>
<td>92</td>
</tr>
<tr>
<td>Difference</td>
<td>(.6:12.0)</td>
<td>(.3:14.6)</td>
<td>(.2:14.0)</td>
<td></td>
</tr>
<tr>
<td># Children</td>
<td>73</td>
<td>84</td>
<td>48</td>
<td>53</td>
</tr>
</tbody>
</table>

* Significantly better than VPA.

P values: CBZ = .0015, LTG = .0003, PHT = .0006

Meador et al. NEJM 2009;360:1597-605

NEAD Age 6 Results: Valproate Group with Lower IQ
Mean IQs (95% Difference CIs from VPA) adjusted for maternal IQ, AED dose, gestational age & folate:

<table>
<thead>
<tr>
<th></th>
<th>CBZ</th>
<th>LTG</th>
<th>PHT</th>
<th>VPA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean IQ</td>
<td>105</td>
<td>108</td>
<td>108</td>
<td>97</td>
</tr>
<tr>
<td>Difference</td>
<td>8</td>
<td>11</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>DCIs</td>
<td>(3:12)</td>
<td>(6:15)</td>
<td>(5:16)</td>
<td></td>
</tr>
<tr>
<td># Children</td>
<td>93</td>
<td>100</td>
<td>56</td>
<td>62</td>
</tr>
</tbody>
</table>

* Significantly better than VPA.

P values: CBZ = .0015, LTG = .0003, PHT = .0006

Dose Dependent Effects: Partial Correlations

<table>
<thead>
<tr>
<th></th>
<th>CBZ</th>
<th>LTG</th>
<th>PHT</th>
<th>VPA</th>
</tr>
</thead>
<tbody>
<tr>
<td>IQ</td>
<td>-.08</td>
<td>.19</td>
<td>-.11</td>
<td>.56*</td>
</tr>
<tr>
<td>Verbal Index</td>
<td>-.03</td>
<td>.12</td>
<td>.06</td>
<td>-.40*</td>
</tr>
<tr>
<td>Non-verbal Index</td>
<td>-.17</td>
<td>.10</td>
<td>-.17</td>
<td>-.42*</td>
</tr>
<tr>
<td>GMI</td>
<td>-.06</td>
<td>.05</td>
<td>-.20</td>
<td>-.30*</td>
</tr>
<tr>
<td>Nepsy Exec Index</td>
<td>-.05</td>
<td>.03</td>
<td>-.10</td>
<td>-.42*</td>
</tr>
<tr>
<td>BRIEF**</td>
<td>-.20</td>
<td>.15</td>
<td>.31</td>
<td>.35*</td>
</tr>
</tbody>
</table>

* Significant correlations; **Lower BRIEF scores better

Other Adverse Concerns for Valproate
- Weight gain
- Hair Loss
- Polycystic Ovarian Like Syndrome
- Drug Interactions
- Cognitive Side Effects
- Potential autism or other behavioral problems from fetal exposure

Options for Valproate
- Generalized Epilepsy
  - About 15% will respond only to valproate compared to lamotrigine or topiramate.*
  - No head-to-head for other options
- Migraine
  - Multiple other options
- Bipolar Disorder & Other Psych Disorders
  - Multiple other options


FDA Warning 6/30/2011
Fetal Valproate Exposure & Cognitive Deficits
Children born to mothers who take the anti-seizure medication valproate...during pregnancy have an increased risk of lower cognitive test scores than children exposed to other anti-seizure medications.

http://www.fda.gov/Drugs/DrugSafety/ucm261543.htm
Impact on Clinical Care and Practice

• Valproate is a poor 1st choice drug for most women of childbearing potential.
• Appropriate informed consent to women should include an outline of risks prior to pregnancy.
• If valproate is employed, dose should be kept as low as possible.
Tumor-related Epilepsy: Algorithm and treatment summary
December 2, 2012

Jorge G Burneo, MD, MSPH
Associate Professor of Neurology and Epidemiology
Co-Director, Epilepsy Program, Western University
London, Ontario, CANADA

Learning Objectives
• To provide a summary and an algorithm for the treatment of tumor-related epilepsy

Epidemiology
• Brain Tumors
• Frequency of epilepsy ~40%
• Low-grade → >75%
• DNET >> ganglioglioma >> low-grade gliomas
• Seizures as presenting symptom → favorable prognostic factor for survival
• Dual pathology:

...epidemiology
• Risk of intractability → 50%....twice as high as other causes
• Longer the duration of epilepsy → worse the outcome

Semiology
Low-grade vs. GBM

Low-grade
• 69% seizures
• Frontal >> temporal > insular > other

GBM
• 42% seizures (presenting symp)
• 62% seizures

Disclosure
Grants: Ontario Brain Institute, Western University, Lawson Research Institute, UCB Canada
Speaker: UCB Canada
Educational activities: UCB Canada, EISAI Canada
Consultant: UCB Canada, GSK Canada
Editorial Board: Can J Neurol Sci, Epilep Behav, Clin Neurol Neurosurg, Rev Neuropsiq
Treatment: General Principles

- Interacico Anti-neoplastics and EIAEDs
- No evidence supporting prophylactic Rx
- Newer AEDs better tolerated
- Radiation and chemo (TMC) decrease seizures: 59% vs. 13% (control)
- Sx for refractory epilepsy (low grade)


What AEDs?

- VPA
- LEV
- ITG/TPM/other

Marion 2000, Privitera 2003; Gamble 2006; Brodie 2007

Algorithm

Seizure / Brain Tumor

Non-Malignant

- AEDs
- Sx free
- Continue with AEDs

Malignant

- Not sx free
- Tumor surgery and AEDs

Valproate: concerns

?-survival

EIAED

Bone Marrow

Jentrik et al, NEJM 2010

Surgical treatment

Timing

Soon!

As much as possible (including hippocampal structures)

Resection beyond lesion

Chang et al, 2010
A Case of Epilepsy Presenting from Civilian Trauma
December 2, 2012
Katherine Noe, M.D., Ph.D.
Mayo Clinic Arizona

Civilian Trauma Case
• 32 year old scientist in excellent health until struck by a car while jogging
• Left frontotemporal hematoma with shift requiring craniotomy evacuation, multiple orthopedic injuries
• In ICU x 3 weeks, followed by outpatient rehab
• Seizures starting post-op week 2

Trauma Case (cont.)
• “Not the same person”
• Irritable, emotionally labile, anxious, depressed
• Short term memory loss, anoma, poor concentration, slowed processing, poor organization
• Unable to return to work, divorced

Trauma Case (cont.)
• Partial complex seizures 15x/month, rare secondary generalization, despite use of 2 AEDs at high doses
• Semiology: confused, expressive and receptive aphasia, alexia, agraphia lasting 1-15 minutes
• Routine EEG: left temporal sharp waves and mild focal slowing left frontotemporal

MRI
Axial FSE T2
Coronal FLAIR
Trauma Case (cont.)
- Referred for video-EEG monitoring 2 years after traumatic brain injury
- Interictal: left frontal, temporal, and central sharp waves
- Ictal: left posterior temporal
- SISCOM: lateralized to left hemisphere, non-localized
- Neuropsychological testing: moderate to severe restriction in naming, mild impairment in verbal memory

Intracranial Electrode Implantation
- Technically difficult implantation due to dense adhesions between dura, brain, cortical vessels

Trauma case (cont.)
- Increased aphasia noted on POD #2
- Taken back to OR for evacuation of fluid collection
- Subsequently tolerated monitoring well

Trauma Case (cont.)
- 4 clinical and 6 electrographic seizures recorded; multi-focal onsets (frontal, anterior + posterior temporal neocortical)
- No resection
- Vagus nerve stimulator placed
- 3 years later continues to have 2-4 partial complex seizures/month on 3 AEDs + VNS
- Unable to work or drive
Occurrence and Risk Factors for Post-traumatic Epilepsy in Civilian Populations
December 2, 2012
Dale C Hesdorffer, PhD
GH Sergievsky Center, Columbia University

Learning Objectives
• To understand the proportion of epilepsy due to traumatic brain injury (TBI) in incident and prevalent cohorts.
• To understand the cumulative risk for epilepsy by TBI severity in civilian populations
• To understand risk factors for post-traumatic epilepsy in civilian populations and risk for specific seizure types

Minimal criteria for brain injury
• Loss of consciousness (even seconds)
• Disturbance of consciousness (amnesia, compromised awareness, dazed)
• Focal neurologic deficit - e.g., hemiparesis, aphasia
• Injury on CT or MRI Imaging (contusion, intracranial hematoma)
• Residual on neuropsychological testing

Traumatic brain injury severity
Glasgow Coma Scale
• Mild Brain Injury     GCS 13-15
• Moderate Brain Injury GCS 9-12
• Severe Brain Injury   GCS 3-8

Sequelaes of Traumatic Brain Injury
• Post concussion syndrome
• Focal neurological deficit
• Cognitive impairment
• Post-traumatic epilepsy
Incidence and distribution of Traumatic Brain Injury

- 180/100,000 to 281/100,000
- Incidence peaks in young adults and in the elderly
- TBI is 1.8 to 2.8 fold more common in males
- Falls and transportation-related accidents predominate, accounting for 63% to 79% of injuries.

Proportion of incident epilepsy by etiology, Rochester, MN 1935-84

Cumulative incidence of unprovoked seizure by TBI severity

Incidence of unprovoked seizures by TBI severity on the GCS

Late Seizures

Proportion of prevalent epilepsy by etiology, Rochester, MN 1940-1980

Cumulative incidence of unprovoked seizure by TBI severity

Incidence of unprovoked seizures by TBI severity on the GCS

Late Seizures

Impact on Clinical Care and Practice

- The increased risk for epilepsy is limited to moderate and severe civilian TBI, which comprises ~5% of all incident and all prevalent epilepsy.
- In people under 35 years of age, TBI increases the risk for GTCS and for CPS, but not for absence seizures.
- Risk factors for epilepsy after TBI include brain contusion, SOH, linear or depressed fracture, LOC/PTA >24 hours, and age ≥35 years.
- The risk for epilepsy after civilian TBI is greatest in the first two years after TBI in most studies except Rochester where the greatest risk for severe TBI persists for 10 years.
Epidemiology of TBI: Risk Factors and Natural History
December 2, 2012
Susan T. Herman, MD
Beth Israel Deaconess Medical Center
Harvard Medical School

Learning Objectives
- Identify common risk factors for post-traumatic epilepsy
- Explore the relationship between early and late post-traumatic seizures
- Describe the natural history of post-traumatic epilepsy and risk of intractable epilepsy

Acute Symptomatic Seizures
- Provoked seizures
- First 1-2 weeks after brain injury
- Marker of severity of underlying disorder

Epileptogenesis
- Initial Precipitating Injury
- Late Seizures
- Recurrent in >80%

Acute Symptomatic Seizures
- Associated with development of epilepsy
- Late seizures occur in 47% of patients with clinical AS
- AS are independent predictor (OR 2.84) for development of late seizures

Disclosure
Name of Commercial Interest
- UCB Pharma
- Lundbeck, Inc.
- Vertex
- Fidelity Biosciences Research Initiative

Type of Financial Relationship
- Research Support, Local PI
- Research Support, Local PI
- Research Support

American Epilepsy Society | Annual Meeting

Hesdorffer et al, Ann Neurol. 1998; 44:908-12
### Seizure Prevention Trials after Traumatic Brain Injury

**Graph:**
- Early PHT vs. placebo
- Early PHT vs. VPA

*Temkin et al., J Neurosurg 1999;91:593-600

### Electrographic Seizures in TBI
- Seizures in critically ill patients often subclinical
- Paralytic or sedative agents
- Concurrent medical illnesses
- Underlying neurological deficit
- Administration of AEDs
- Prospective study of 91 patients with severe TBI
  - EEG monitoring for 7-10 days
  - All patients received prophylactic phenytoin
  - 22% had seizures
  - 57% only subclinical
  - 6/6 patients with status epilepticus died

*Temkin et al., J Neurosurg 1999;91:593-600
*Vespa et al., J Neurosurg, 1999;97:750-760

### Early PTS and Epilepsy
- Retrospective analysis
- 140 patients with moderate to severe TBI, CEEG
- 16 patients volumetric MRI, acute and 6 months
- 6 patients with early seizures, 10 age and GCS-matched patients with TBI, no seizures
- Patients with seizures showed greater hippocampal atrophy (21 +/- 9 vs 12 +/- 6%, p = 0.017), especially ipsilateral to the electrographic seizure focus


### Intercital Epileptiform Discharges
- Animal model of TBI
- IEDs and brief electrographic Sz precede clinical seizures
- Inadequately studied in humans
- Non-standardized timing and methods for EEG
- Most utilize routine EEG
  - IEDs are rare in adults, even those with acquired brain injuries
  - Presence of IEDs +/or focal slowing at 1 month associated with 3.5-fold higher risk of developing late seizures (n=137, 18 with epilepsy)


---

**Graph:**
- Electrographic seizure focus
- Inadequately studied in humans
- Presence of IEDs +/- focal slowing at 1 month associated with higher risk of late seizures

Post-traumatic Epilepsy
Military Experience (Korea)

<table>
<thead>
<tr>
<th>Category</th>
<th>Characteristics</th>
<th>Incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Blow to head w/o LOC</td>
<td>7</td>
</tr>
<tr>
<td>II</td>
<td>Blow to head w/ LOC &lt;6 hr</td>
<td>10</td>
</tr>
<tr>
<td>III</td>
<td>Penetration of dura w/o apparent brain damage</td>
<td>39</td>
</tr>
<tr>
<td>IV</td>
<td>Dura penetration w/o LOC and no neurologic deficit</td>
<td>20</td>
</tr>
<tr>
<td>V</td>
<td>Dura penetration with evident neurologic deficit</td>
<td>51</td>
</tr>
<tr>
<td>VI</td>
<td>Penetration of dura and brain of profound degree</td>
<td>57</td>
</tr>
</tbody>
</table>

Caveness, Epilepsia 1976;17:207

Military Head Injury

- Iraq and Afghanistan veterans
  - 6.7-14.9% diagnosed with or self-reported TBI
- Many with recurrent mild TBI
- Walter Reed Army Medical Center trauma admissions

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>% TBI</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Penetrating</td>
<td>100</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blunt trauma</td>
<td>56.6</td>
<td>58.1</td>
<td>32.6</td>
<td>9.3</td>
</tr>
<tr>
<td>Blast trauma</td>
<td>54.3</td>
<td>67.5</td>
<td>27.8</td>
<td>4.6</td>
</tr>
</tbody>
</table>


TBI and Psychogenic Nonepileptic Events

- Retrospective study of EMU admissions to VAMC
- Psychogenic nonepileptic event diagnosis
  - 26 % of 726 civilians
  - Average 12.5 months to diagnosis
  - 25% of 203 veterans
  - Average 60.5 months to diagnosis
  - 4x greater AED exposure
  - 58% thought to be related to TBI


Natural History of PTE

- 86% of patients with 1 late unprovoked post-traumatic seizure experience a second seizure within 2 years
- 25-40% seizure remission rate in non-penetrating TBI
- 39 selected adult patients (25 male) with moderate TBI
  - 36% required more than 1 AED trial
  - 8% failed multiple AEDs
- TBI associated with increased risk of refractory epilepsy
- 27% of patients with TBI and PTE died at 8 to 15 years after injury vs. 10% of matched TBI-only patients


Predictors of Intractable Epilepsy

- Early seizures are associated with higher risk of PTE
- Pathogenic significance remains unclear
- Further exploration of IEDs as risk factor / biomarker is warranted
- PTE is associated with higher risk of refractory epilepsy
- Further studies of PTE needed to better understand natural history


Summary
Epileptogenesis after TBI: Biomarkers and Variability

December 2, 2012

Samuel Wiebe, MD
University of Calgary

Learning Objectives

• To explore biomarkers for post-traumatic epilepsy
  • Biochemical, genetic, imaging, clinical
• To explore the heterogeneity of risk for post-traumatic epilepsy

Nature-Nurture in Epilepsy

No Endophenotype for PTE

• If Temporal lobe epilepsy, 50% have MTS
• MRI gliotic scar and cortical hemosiderin
• Routine EEG not helpful
• Video-EEG
  — Seizures are most commonly focal (90%)
    • Temporal 54%
    • Frontal 33%
  — Selection bias

Jennett et al. Epilepsia 1975; Diaz-Arrastia et al. Epilepsia 2009

Haptoglobin as a biomarker of PTE

• Neutralizes and removes extracellular hemoglobin
• Hp increased after TBI
• Hp 1-1 more effective than Hp 2-2
• Ratio of Hp 2-2 to Hp 1-1 increased in generalized epilepsy
• Marker for development of PTE?

Anderson et al. E&B 2009
**Serum Haptoglobin Phenotypes**

*case-control study*

- Percent with phenotype
  - Haptoglobin 1-1: 22
  - Haptoglobin 2-2: 34
  - Haptoglobin 2-1: 43

- Anderson et al, E&B 2009

**APOE-ε4**

- Produced in response to injury
- Antioxidant, anti-inflammatory, anti-excitotoxic
- ε4 allele less favourable outcome

**APOE genotype as a marker**

*cohort study n=106*

- Percent with genotype
  - APOE ε4: 43
  - APOE ε2: 22
  - APOE ε3: 31

- Diaz-Arrastia et al, Arch Neurol 2003

**MRI- endophenotypes?**

- N=135, PTE 20, MRI 4-6 months
- Gliotic wall surrounding hemosidering
- Probability of PTE at 10 years

- Messori et al, Epilepsia 2005

**MRI endophenotypes?**

*DTI*

- Fractional Anisotropy Ratio

- Gupta et al, Epilepsia 2005
Maturational aspects of epilepsy mechanisms

% Adult Function

Sanchez & Jensen, Epilepsia 2001

Effect of age on PT seizure susceptibility

Adapted from Jyoti et al, Neurosci Lett 2009

Heterogeneous study methods

Methods

• Population
  – Civilian, military, adult, paediatric, inpatient, outpatient, trauma centre, rehab centre
• Criteria
  – All TBI, CT head, GCS cut-off, specific study criteria
• Seizure diagnosis
  – Clinic, questionnaire, chart, telephone, MD, interviewer
  – Criteria: Late? Early? Epilepsy?

Implications for Clinical Practice

• New biomarkers of risk are promising, in particular MRI techniques
• No definitive genetic biomarkers yet
• Variability of methods produces heterogeneous results of risk of PTE
• Assess carefully when estimating risks for individual patients
Epileptogenesis and Treatment
Jerome Engel, Jr., MD, PhD
Jonathan Sinay Distinguished Professor of Neurology, Neurobiology, and Psychiatry & Biobehavioral Sciences
David Geffen School of Medicine at UCLA

Disclosures
NIH NINDS grants
R01 NS02808
R01 NS33310
P20 80181

Elsevier
Wolters Kluwer
Royalty
Royalty

Wiley-Blackwell
MedNet
Best Doctors
ION
Oxford
Medicine
Best Doctors
ION
FDA
Consultant
Consultant

Learning Objectives
1. Understand possible mechanisms of post traumatic epileptogenesis
2. Understand value of biomarkers in developing antiepileptogenic treatments

Epileptogenesis after Trauma
• Cell death
• Neuronal reorganization
• Enhanced excitation
• Decreased and enhanced inhibition
• Enhanced tendency to synchronization

Engel, J Jr. EEG J 76:296-316, 1990
Engel, J Jr. Seizures and Epilepsy. FA Davis, 1989
Treatment

- Discovery and validation of antiepileptogenic interventions are impeded by the prohibitive cost of screening and clinical trials
- The variable incidence of PTE after severe head trauma, and the late-onset of seizures that can occur over 10 years after injury make huge animal and patient populations necessary and require exceedingly long follow-up
Biomarkers

Dynamic changes that indicate the presence of an epileptogenic process with a sufficiently high degree of reliability to warrant intervention

- Biomarkers of epileptogenesis
- Biomarkers of epileptogenicity

Biomarkers of Epileptogenesis

- Identify the development of brain tissue capable of generating spontaneous epileptic seizures
- Identify the progression of an epileptic condition after it has developed

Biomarkers of Epilepsy Development

- Predict epilepsy in patients with risk factors
  - genetic predisposition
  - prolonged febrile seizure
  - head trauma
  - intracranial infection
  - brain lesion
- Institute antiepileptic intervention

Biomarkers of Epilepsy Development

- Create cost-effective rapid-throughput models for screening potential antiepileptogenic interventions
- Identify subjects to enrich clinical trials of potential antiepileptogenic interventions

Target Mechanisms

- Cell loss (e.g., hippocampal atrophy)
- Axonal sprouting
- Synaptic reorganization
- Altered neuronal function (e.g., gene expression profiles, protein products)
- Neurogenesis
- Altered glial function and gliosis
- Inflammatory changes
- Angiogenesis
- Altered excitability and synchrony

Potential Biomarkers

- Hippocampal changes on MRI
- Interictal spike features, including fMRI
- Pathological high-frequency oscillations (pHFOs)
- Excitability – TMS
- AMT-PET imaging
- Gene expression profiles
Epilepsy From A Military Experience
December 2, 2012

Sara Schrader, MD
Major, USAF, MC
JWM Neurology, PC Indianapolis, IN

Case Presentation

• 28yo left-handed male Marine
• Shot in the head by a sniper while supporting Operation New Dawn in Iraq September 2010
• Underwent craniotomy and debridement in theater
• Treated with levetiracetam 500mg BID for seizure prophylaxis

Case Presentation

• Transferred to National Naval Medical Center and had second craniotomy
• Had left hemisphere cranioplasty at Brooke Army Medical Center January 2011

Disclosure

Nothing to disclose
Case Presentation

- Residual deficits of spastic right hemiplegia, right hemisensory deficit, and right quadrantanopia
- Had first seizure March 2011
  - Right side stiffens and head turns to right, followed by generalized convulsion
- Levetiracetam dose escalated over time due to recurrent seizures

Impact on Clinical Care and Practice

- Should AED prophylaxis be used after head trauma prior to the first seizure?
- Is AED prophylaxis effective in posttraumatic epilepsy?

- Had 1-2 seizures per month as of March 2012 while taking levetiracetam 1500mg BID
- Oxcarbazepine added to regimen and titrated up to 600mg BID
- Dose increased to 900mg BID after recurrent seizures April 2012
Global War on Terror (GWOT)

- Iraqi-9 years of conflict March 2003-December 2011
  - Operation Iraqi Freedom (OIF) Began March 2003
  - Operation New Dawn (OND) Began September 2010
- Afghanistan- Oct 2001
  - Operation Enduring Freedom (OEF)

1. Overview of current military TBI
   - Combat TBI
   - Gathering the data
     - In Theatre Diagnosis
       - Mandated Screening
       - Neurology Teleconsult
       - Blast Gauge
     - Exit from Service
       - VA Screen

OEF/OIF Patient Characteristics

- Long War
- Multiple Deployments
- Multiple Blast Exposures
- Chronic Pain
- Under Stress for Prolonged Periods of Time
Current Injury Etiology

- Leading cause of combat injuries OIF/OEF
  - 74% Explosions, primarily improvised explosive devices
  - 18-20% Gunshot wounds
- Leading causes Vietnam
  - 65% Explosions
  - 35% Gunshot wounds

Owens et al (2012)

Military vs. Civilian TBI

- Combat troops injured by blast explosive brisance
  - Acute polytrauma, no civilian equivalent
  - Neurological effects may differ from other causes of TBI
- Population is different
  - Unique population Unifying characteristics (age, gender, enlisted, fitness standard, absence of alcohol, illicit drug or criminal behavior, treatment in choreographed continuum of care)
- Risk from mild TBI in this setting is unknown

TBI Screening in-theatre practice guidelines

- Military Leaders required to identify personnel involved in a mandatory event and conduct screening, ensure reporting, and refer anyone with positive screen for full medical evaluation
- Mandated Screening using Military Acute Concussion Examination (MACE)
  - MACE brief screen that combines:
    - acute injury characteristics and symptoms
    - brief validated cognitive screening
Mandatory Events Requiring Evaluation

- Any Service Member in a vehicle associated with a blast event, collision or rollover
- All within X meters of a blast (inside or outside)
- Anyone who sustains a direct blow to the head
- Command directed, especially with repeated exposures to blasts

Army Knowledge Online (AKO) teleconsultation

Centralized system for deployed military care providers to receive expert recommendations on triage and disposition

Quantities of Military Teleconsults Requested per Calendar Year

Consultant recommendations

Diagnoses, initial and final

Blast Exposure DARPA Blast Gauge

- Measures blast exposure
- Recording 20 msec per episode and then resets itself
- Measures blast wave form, duration, change in air pressure, head axis acceleration
- Data can be downloaded via mini-USB port
- Data stored in a central database
- Currently being used on 11,000 service members in Afghanistan

Status lights:

Yurkiewicz et al 2012

Yurkiewicz et al 2012

Jeff Rogers, PhD
MTO, DARPA
TBI in Veterans who seek VA care
April 2007-August 2012

- 1,515,707 OEF/OIF/OND Veterans have left active duty and become eligible for VA health care since FY 2002
- 834,463 (55%) of these Veterans obtained VA health care
- 647,197 Screen positive for possible mild TBI
- 128,617 (19.9%) are screen positive for TBI
- 51,159 have diagnosis of TBI (7.9 % of initial possible screens)

Sources:
http://vssc.med.va.gov/tbireports/comprehensivetbi.aspx

Posttraumatic epilepsy following craniocerebral missile wounds in armed conflicts during the 20th century

<table>
<thead>
<tr>
<th>Conflict</th>
<th>Author(s), year</th>
<th>No. of patients</th>
<th>Posttraumatic epilepsy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>WW I</td>
<td>Credner, 1930</td>
<td>1990</td>
<td>38</td>
</tr>
<tr>
<td>WW I</td>
<td>Ascroft, 1941</td>
<td>317</td>
<td>35</td>
</tr>
<tr>
<td>WW I</td>
<td>Caviness, 1966</td>
<td>82</td>
<td>50</td>
</tr>
<tr>
<td>WW II</td>
<td>Russell &amp; Whitty, 1952</td>
<td>820</td>
<td>43</td>
</tr>
<tr>
<td>Korean War</td>
<td>Russell &amp; Whitty, 1952</td>
<td>820</td>
<td>43</td>
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<td>Korean War</td>
<td>Caveness et al., 1962</td>
<td>211</td>
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<tr>
<td>Korean War</td>
<td>Taylor &amp; Kretschmann, 1971</td>
<td>474</td>
<td>50</td>
</tr>
<tr>
<td>Korean War</td>
<td>Caveness et al., 1979</td>
<td>1135</td>
<td>34</td>
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<tr>
<td>Vietnam War</td>
<td>Salazar et al., 1985, 1987</td>
<td>520</td>
<td>34</td>
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<td>Vietnam War</td>
<td>Salazar et al., 1999</td>
<td>520</td>
<td>34</td>
</tr>
<tr>
<td>Iran-Iraq</td>
<td>Aarabi, 1990</td>
<td>489</td>
<td>32</td>
</tr>
<tr>
<td>Lebanon</td>
<td>Salazar et al., 1999</td>
<td>80</td>
<td>30</td>
</tr>
</tbody>
</table>

Lowenstein 2009 - adapted from Salazar 1999

Korean and Vietnam War Veterans
Risk with other TBI severity

- 53% risk with penetrating TBI
- 10-25% closed head injury (combat) with positive brain imaging
- 5% in moderate CHI without imaging findings

Chen et al 2009

Vietnam PTE Latency

- Report of the Vietnam Head Injury Study showed that the overall seizure occurrence 15 years after head injury was 53% with the vast majority developing epilepsy (Salazar 1985)
- Recent Vietnam Head Injury Study showed that 12.6% of Veterans with TBI had initial onset of epilepsy more than 14 years after their injury (Raymont 2010)

Recent Conflict (Iran-Iraq War)

- 32% with penetrating TBI developed epilepsy during an average of 39.4 months of follow-up
- 489 patients with penetrating head trauma over 8 year period followed for up to 154 months
- 32% (157) developed epilepsy during follow-up period of almost 13 years
  - Latency
    - 6 months-63 72% in first year
    - 12 months-50
    - 24 months-17
    - 48 months-16
    - 111 months-8 95% in first four years

Aarabi et al 2000
3. Understand the system of care established for veterans with epilepsy

- Numbers of Veterans with epilepsy
- Epilepsy Centers of Excellence (ECoE)
- Veterans receive care for epilepsy
  - DoD and civilian
  - Non-epileptic seizures in veterans

Epilepsy population demographics

- About 85,000 Veterans treated at VA are diagnosed with epilepsy or seizures
- 20% were seen within a Medical Center with an Epilepsy Center
- 75% are age 50 and older
- 7% are female
- Many medically and surgically refractory
- Non-epileptic seizures

Non-epileptic seizures within Veterans in the VA

- FY 12 EMU diagnosis from 14 Epilepsy Center of Excellence sites
- 652 total EMU admissions
- 192 (29%) confirmed diagnosis of PNES

Establishment of Epilepsy Centers of Excellence (ECoE)

- Public Law 110-387: Veterans Mental Health and Other Care Improvements Act of 2008
- Centers must:
  - link to existing VHA Polytrauma Centers
  - link to academic centers and conduct research
  - be established by a Peer Review Panel
  - be involved with education and fellowship training
- Funding Cycle October 2008-September 2013
ECOE Goals

- Delivery the highest quality care to veterans with epilepsy, regardless of their geographic location
- Streamline epilepsy referrals to sites with expertise and services
- Take epilepsy care to veterans in remote areas
- Promote outreach and educational efforts
- Provide an efficient and cost-effective mechanism of care delivery
- Establish a national clinical database

Impact on Clinical Care and Practice

- Army veterans who served in Iraqi, especially in the early years, have sustained more TBI than other services
- Risk of developing PTE from mild TBI in OEF/OIF veterans remains unknown

We wish to acknowledge and thank veterans who have made enormous sacrifices for our country

Medical Evacuation runway at Landstuhl Army Hospital, Germany
AEDs as prophylaxis for Posttraumatic epilepsy

December 2, 2012

Marc A. Dichter, MD, PhD
University of Pennsylvania
Philadelphia, PA

Learning Objectives

• Preventing epilepsy in those with known risks (such as TBI) is critically important
• TBI may produce localized changes in the brain that create brief, localized seizures, and these may be suppressible by standard AEDs
• Seizures under some circumstances produce damage and foster further seizures
• New AEDs with new mechanisms of action are available that may suppress early post-TBI seizures
• Animal data exist that indicate the feasibility of this approach in other paradigms

Rationale for using anti-seizure drugs now

• AEDs are available, we have extensive experience using them, are relatively safe, are known to be effective in suppressing seizures at least, and in some cases, also suppressing some epilepsy associated changes
• Pilot clinical trials, and even a small network of trial centers, can be started now to develop infrastructure, techniques (including long term monitoring, etc), possible biomarkers, and a better understanding of the process of epileptogenesis in man after different risks

 Disclosure

Name of Commercial Interest
None

Type of Financial Relationship
None

The argument

• Seizures develop after TBI
• The latency is unknown – current ideas are all based on clinical seizure observations
• One hypothesis is that TBI is associated first with small, localized seizures that are not visible clinically or with routine scalp EEGs and that these seizures produce increased damage and other changes associated with the development of PTE
• Remember the kindling paradigm
• It is likely that an anti-seizure drug could suppress these
• There are no good data to support or refute this argument
• More than 15 effective and relatively safe AEDs are available to test this concept
• In several epilepsy models (not PTE), early treatment can prevent subsequent epilepsy
• It is certain that doing nothing will not solve this problem

Post-traumatic epilepsy

Which of these are critical for epileptogenesis?
Epileptogenesis

- Some anti-seizure drugs can interrupt kindling (PHB, VPA, LTG, TPM, LEV, LAC, VGB, BZDs)
- Ethosuximide treatment prevents epilepsy in WAG rats (Blumenfeld et al, Epilepsia 2008)
- TTX and Gabapentin prevent hyperexcitability in undercut cortex – a slightly different model (Li, Graber et al, Neurobiol of Dis 2012)
- Cooling cortex around TBI prevents epilepsy (D’Ambrosio et al, Ann Neurol, 2012)
- mTOR inhibitors block epilepsy in TS mice and may also work in status epilepticus model (Zong LH, Xu L, Gutmann DH, Wong M, Ann Neurol 2008)
- (Liang et al, Neurobiol Dis 2010)

Proofs of concept

S/W seizures in WAG rats

Ethosuximide treatment “prevents” epilepsy

Note that even after 3 months, treated rats do not “catch up” to untreated subjects

Posttraumatic epilepsy induced by FPI in the rat

Paired scalp-EEG and epidural ECoG: grade 1 seizures

Note: lack of EEG seizure

Limited to cortical focus

Scalp

Lack of scalp seizure

1s
All AEDs are not alike in their possible actions

• Current AEDs have multiple mechanisms of action
• Some work well for neuropathic pain
• Some are sedating; other’s are not
• Some suppress abnormal network activity in AD models; others are ineffective
• Need to examine multiple AEDs to assess effectiveness in TBI models

Conclusion

• Epilepsy after TBI is an important problem that needs to be solved
• More basic research is needed, including testing newer AEDs in TBI models
• More clinical research is also needed to determine the phenomena and mechanisms associated with the epileptogenic process in man
• AEDs may prove useful in suppressing epileptogenesis if used early and appropriately
• Other strategies involving drugs that do not directly suppress seizures or devices are likely to be useful as well

Impact on Clinical Care and Practice

• Individuals with moderate to severe TBI need to be monitored for epilepsy development
• Acute continuous scalp, subgaleal, and intracranial EEG monitoring may reveal subclinical seizures that are amenable to treatment early
• Early treatment with AEDs may reduce the incidence of PTE
• More basic and clinical research is needed in this area
• Doing nothing will definitely not solve this problem
AED Prophylaxis Does NOT Work in Posttraumatic Epilepsy

December 2, 2012

Patrick Kwan, MD, PhD
University of Melbourne, Melbourne, Australia
Chinese University of Hong Kong, Hong Kong

Learning Objectives

• Systematic reviews of clinical trials of AED prophylaxis for early and late posttraumatic seizures
• Highlights from individual studies

Classification of TBI-related Seizures

• Seizures ≤7 day = acute symptomatic (provoked) seizures
  – <24 hours = immediate seizures
  – 24 hrs to 7 days = early seizures
• Seizures >7 days = late (unprovoked) seizures = post-traumatic epilepsy

<table>
<thead>
<tr>
<th>Study</th>
<th>AED(s)</th>
<th>No.</th>
<th>Follow-up (mo)</th>
<th>% with seizures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Servit 1981</td>
<td>PB, PH</td>
<td>168</td>
<td>6-156</td>
<td>2 25</td>
</tr>
<tr>
<td>Wohls 1979</td>
<td>PH</td>
<td>62</td>
<td>6-72</td>
<td>10 50</td>
</tr>
<tr>
<td>Young 1979</td>
<td>PH</td>
<td>84</td>
<td>12</td>
<td>6 2-31</td>
</tr>
<tr>
<td>Murr 1980</td>
<td>PB</td>
<td>83</td>
<td>24</td>
<td>2 7-16</td>
</tr>
<tr>
<td>Murr 1992</td>
<td>PB, PHT</td>
<td>390</td>
<td>12</td>
<td>2 7-16</td>
</tr>
<tr>
<td>Price 1980</td>
<td>VPA</td>
<td>143</td>
<td>24</td>
<td>0 15-55</td>
</tr>
</tbody>
</table>

RCT: Phenytoin to Prevent PTE

• Patients with severe TBI (predicted seizure risk ≥20%)
• Double-blind randomization to receive within 24 hrs of injury
  – Placebo, or
  – Phenytoin (i.v. then oral) for 12 months
• TDM to maintain therapeutic serum concentration
  – Maintained in >70% patients
  – Within therapeutic range in 75% of patients who had late seizures

Disclosure

Eisai
Consultancy, research contract

GSK
Consultancy, research contract

Pfizer
Research contract

UCB Pharma
Speaker, research contract

American Epilepsy Society | Annual Meeting 2012
Early Seizures

Late Seizures (PTE)

Prospective Controlled Studies of AED for Prophylaxis of Seizures after Severe Head Trauma

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment groups</th>
<th>Random</th>
<th>AED (n)</th>
<th>Control (n)</th>
<th>Cochrane</th>
<th>Begh AAN</th>
</tr>
</thead>
<tbody>
<tr>
<td>McGeeen 83</td>
<td>Y</td>
<td>PHT (84)</td>
<td>Placebo (80)</td>
<td>2002, 2003</td>
<td>✔️ ✔️ ✔️</td>
<td></td>
</tr>
<tr>
<td>Young 83</td>
<td>Y</td>
<td>PHT (119)</td>
<td>Placebo (95)</td>
<td>2002, 2003</td>
<td>✔️ ✔️ ✔️</td>
<td></td>
</tr>
<tr>
<td>Temkin 80</td>
<td>Y</td>
<td>PHT (208)</td>
<td>Placebo (196)</td>
<td>2002, 2003</td>
<td>✔️ ✔️ ✔️</td>
<td></td>
</tr>
<tr>
<td>Temkin 99</td>
<td>Y</td>
<td>VPA (347)</td>
<td>PHT 1 wk (132)</td>
<td>2002, 2003</td>
<td>✔️ ✔️ ✔️</td>
<td></td>
</tr>
<tr>
<td>Maralka 92</td>
<td>Y</td>
<td>PB (50)</td>
<td>None (76)</td>
<td>2002, 2003</td>
<td>✔️ ✔️ ✔️</td>
<td></td>
</tr>
<tr>
<td>Peckahde 91</td>
<td>Quasi</td>
<td>PHT (34)</td>
<td>None (52)</td>
<td>2002, 2003</td>
<td>✔️ ✔️ ✔️</td>
<td></td>
</tr>
<tr>
<td>Servi 81</td>
<td>N</td>
<td>PHT+PB (143)</td>
<td>None (24)</td>
<td>2002, 2003</td>
<td>✔️ ✔️ ✔️</td>
<td></td>
</tr>
</tbody>
</table>

CBZ: Carbamazepine, UTD: intracerebral PB, phenobarbitol, PHT: phenytoin

Early Post-traumatic Seizures

AED to Prevent PTE: The Hopefuls

- Previously tested AEDs have many adverse effects
- Newer AEDs have not been adequately tested
- The “antiepileptogenic” argument
  - Should test AEDs shown to have antiepileptogenic effects in animal models
Prospective Controlled Studies of AED for Prophylaxis of Seizures after Severe Head Trauma

<table>
<thead>
<tr>
<th>Study</th>
<th>Random</th>
<th>AED (n)</th>
<th>Control (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>McQueen 83</td>
<td>Y</td>
<td>PHT (64)</td>
<td>Placebo (60)</td>
</tr>
<tr>
<td>Houn 83</td>
<td>Y</td>
<td>PHT (119)</td>
<td>Placebo (95)</td>
</tr>
<tr>
<td>Glöckner 83</td>
<td>Quasi</td>
<td>CBZ (75)</td>
<td>Placebo (70)</td>
</tr>
<tr>
<td>Trenk 90</td>
<td>Y</td>
<td>PHT (208)</td>
<td>Placebo (196)</td>
</tr>
<tr>
<td>Trenk 99</td>
<td>Y</td>
<td>VPA (247)</td>
<td>PHT 1 wk (132)</td>
</tr>
<tr>
<td>Manaka 92</td>
<td>Y</td>
<td>PB (50)</td>
<td>None (76)</td>
</tr>
<tr>
<td>Pechare 91</td>
<td>Quasi</td>
<td>PHT (34)</td>
<td>None (52)</td>
</tr>
<tr>
<td>Serri 81</td>
<td>N</td>
<td>PHT+PB (143)</td>
<td>None (24)</td>
</tr>
</tbody>
</table>

Jones 2006: N LEV (52)  History: PHT (41)
Kern 2012: N LEV (66)  None (60)

Phase 2 Nonrandomized LEV Study for PTE

- Primarily to evaluate safety and feasibility
- 6-87 years old with severe TBI. All given PHT for 1 week
- Treatment groups:
  - Presented <8 hours → LEV 55mg/kg/d for 30 days (n=66)
  - Presented 8-24 hours → No treatment (n=60)
- Followed up to 24 months
- 12% stopped LEV early
- Mortality: 10.9% treated adults vs. 7.5% untreated adults

RCT VPA to Prevent PTE

![RCT VPA to Prevent PTE: No Good](image)

- VPA 6 mo (n=120)
- VPA 1 mo (n=127)
- PHT 1 wk (n=132)

Ph 0.19

RCT VPA to Prevent PTE: More Harm?

![RCT VPA to Prevent PTE: More Harm?](image)

- VPA 6 mo (n=120)
- VPA 1 mo (n=127)
- PHT 1 wk (n=132)

Ph 0.07
Conclusion

• Prophylactic AEDs reduced acute symptomatic seizures after severe TBI but not posttraumatic epilepsy
• Antiepileptogenic effects in animal models have not been translated to human evidence
• Potential harm with AEDs outweighs benefits
  – Intrinsic adverse effects
  – Deleterious effects on brain recovery
• AED prophylaxis does NOT work in posttraumatic epilepsy
Case: Refractory Epilepsy From Trauma
December 2, 2012

Eric H. Kossoff, MD
Johns Hopkins Hospital
Baltimore, Maryland

A sadly not unusual case...

- 4 month old boy shaken by a babysitter
- Seizures within hours of the injury leading to hospitalization
  - Convulsive, lasting several seconds
- Treated with intravenous phenobarbital with initial resolution

Seizures Become Intractable

- Daily seizures shortly after discharge
- Several medications tried over the next few months
  - phenobarbital, oxcarbazepine, levetiracetam
- At 8 months of age, develops new onset atonic seizures, ~10 clusters per day

Disclosure

Nutricia, Atkins Nutritionals, Elsai, Charlie Foundation, Epilepsy Foundation

Scientific Advisory Board Member

American Epilepsy Society | Annual Meeting 2012
Infantile Spasms

- Treated with ACTH then topiramate with only modest benefit
- 50% reduction in spasms using valproate @ 40 mg/kg/day
- Admitted at 21 months of age to begin the ketogenic diet

Recent Course

- Improvement occurred with combination diet and valproate after several months
- EEG improves: dietary therapy discontinued at 4 years of age
- Development improved, but still has modest motor and language delays

NAT and Infants: High Risk of Epilepsy

- Table 8: Multivariate Logistic Regression Model; Risk of Early First Epileptic Seizures (EFS) in Children

Impact on Clinical Care and Practice

- Always consider abuse in any infant with new onset seizures and subdural hemorrhage.
- Seizures can be both refractory and may develop into infantile spasms.
- Consider nonpharmacologic approaches if medication trials are unsuccessful.
Imaging and EEG in Post-traumatic Epilepsy

Michael R. Sperling, M.D.
Thomas Jefferson University
Philadelphia, PA

Learning Objectives

Discuss the utility of EEG and neuroimaging techniques in diagnosing post-traumatic epilepsy

Discussion how EEG and neuroimaging are used to assess prognosis in post-traumatic epilepsy

Diagnosis

- Diagnosis is clinically driven
- Reliance upon history
- Interictal EEG may aid in confirming clinical suspicion
  - Interictal spikes, focal slow waves, normal
- Ictal EEG may be necessary to establish diagnosis
  - Verify diagnosis of epileptic seizure
  - Verify diagnosis of psychogenic seizure or other non-epileptic event, e.g., syncope

Interictal EEG

Interictal spikes consistent with frontal or temporal contusions

EEG may suggest another etiology
Ictal EEG-Video

MRI
- Provides evidence for the presence of a structural lesion
  - Supports presumed diagnosis of post-traumatic epilepsy
  - Location of lesion may be typical for PTE
    - Frontal, temporal or occipital pole
    - Beneath a depressed skull fracture
    - Establishes presence of blood or hemosiderin
    - If atypical, may lead to questioning diagnosis

CT: Contusion

MRI: Contusion

MRI

Multimodal Imaging

Certain MRI findings may lead to questioning diagnosis of PTE
MRI Lesion and PTE

- Lesion location and development of PTE
  - Cortical vs subcortical vs both
  - Single vs multiple lesions
  - Subdural hematoma vs intraparenchymal lesion
- Presence of hemosiderin and development of PTE
  - Location and prevalence impair accurate assessment
  - Walled vs incompletely walled lesions

Cumulative Probability of Developing PTE at 60 Months (20/184)

<table>
<thead>
<tr>
<th>Variables</th>
<th>No. with PTE</th>
<th>Prob at 60 mo (%)</th>
<th>95% CI (%)</th>
<th>p Value (log-rank test)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sequelae of sSDH-C</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>33</td>
<td>39.13</td>
<td>19.19-59.06</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No</td>
<td>112</td>
<td>9.82</td>
<td>4.31-15.33</td>
<td></td>
</tr>
<tr>
<td>4G MRI lesion versus</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SDH only</td>
<td>21</td>
<td>4.76</td>
<td>0-13.87</td>
<td></td>
</tr>
<tr>
<td>HG lesions only</td>
<td>29</td>
<td>24.14</td>
<td>8.56-39.71</td>
<td>0.067</td>
</tr>
<tr>
<td>G only</td>
<td>9</td>
<td>11.11</td>
<td>0-31.64</td>
<td>0.508</td>
</tr>
<tr>
<td>H only</td>
<td>33</td>
<td>2.66</td>
<td>0-14.2</td>
<td>0.824</td>
</tr>
<tr>
<td>HG lesions + G</td>
<td>34</td>
<td>17.65</td>
<td>4.83-30.46</td>
<td>0.167</td>
</tr>
</tbody>
</table>

SDH-C: subdural/contusion; H: hemosiderin; G: gliosis

Incomplete vs Complete Wall Around Hemosiderin Deposit

Blood-Brain Barrier and PTE

- sLORETA identified delta and contrast enhancement with MRI
  Tomkins et al. JNHP 2012

Diffuse Axonal Injury

- Effect on cortical connections
  Paterakis. J Trauma 2000

MRI Ascertainment of Lesions

- A. Small hemorrhagic lesion in left occipital lobe
- B. DWI shows same lesion
- C. Trace map of diffusion shows same lesion
- D. Lattice index (fractional anisotropy) shows decreased anisotropy in left internal capsule and anterior callosum

Arfanakis et al. AJNR 2002
Blood-Brain Barrier Disruption and PTE

- 32 patients with head trauma – 17 had PTE
- Patients studied at varying intervals after trauma – 5 days to 18 years, though most late
- 80% of patients with PTE had MRI lesion
- 30.8% of patients without PTE had MRI lesion
- 76.9% of patients with PTE had BBB disruption vs. 33.3% of patients without PTE (p < 0.05)
- Volume of BBB disruption was significantly larger in patients with PTE (9.8 ± 2.6 vs. 1.7 ± 0.6 cm³, p = 0.001)

Tomkins et al. JNNP 2012

Relative Risk of PTE in 137 Patients

<table>
<thead>
<tr>
<th>Variables</th>
<th>Relative risk</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early seizures</td>
<td>8.58</td>
<td>2.87-25.65</td>
</tr>
<tr>
<td>Single CT lesion</td>
<td>3.43</td>
<td>1.29-9.57</td>
</tr>
<tr>
<td>Focal EEG</td>
<td>3.49</td>
<td>1.10-11.65</td>
</tr>
<tr>
<td>GCS</td>
<td>0.93</td>
<td>0.30-2.96</td>
</tr>
</tbody>
</table>

Angeleri F et al. Epilepsia 1999

EEG and Brain Volume Loss in ml Vietnam Series

<table>
<thead>
<tr>
<th>EEG and Brain Volume Loss in ml Vietnam Series</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EEG</strong></td>
</tr>
<tr>
<td>---------------</td>
</tr>
<tr>
<td>Abnormally slow</td>
</tr>
<tr>
<td>(36%) (30%) (14%) (21%)</td>
</tr>
<tr>
<td>Epileptiform with or without slowing</td>
</tr>
<tr>
<td>(14%) (22%) (14%) (47%)</td>
</tr>
</tbody>
</table>

Jabbari et al. Electroenceph Clin Neurophys 1986

Management

- Antiepileptic drugs – mainstay of therapy
- Surgery – for medically refractory cases
  - Best prognosis with single lesion
  - Multifocal EEG probably worse prognosis
  - History of trauma or other injury in adults associated with better surgical outcome (Mathern et al)
  - Role of multimodal assessment tools to be defined

Jabbari et al. Electroenceph Clin Neurophys 1986
Impact on Clinical Care and Practice

- EEG and MRI are used to aid in diagnosis of postraumatic epilepsy
- Different techniques elucidate different lesion types
  - Lesion type influences risk of PTE
  - Provide data to identify those at risk for developing PTE
- May be used to identify candidates for therapeutic intervention, e.g., anti-epileptogenesis
Traumatic Brain Injury and Psychogenic Seizures

12/2/2012

Martin Salinsky M.D.
Portland VAMC Epilepsy Center of Excellence
Oregon Health & Science University
Portland, Oregon

American Epilepsy Society | Annual Meeting

Psychogenic Non-Epileptic Seizures (PNES)

- Transient alterations in behavior resembling an epileptic seizure but *not* due to paroxysmal neuronal discharges;
  - without other physiologic abnormalities
  - with probable psychological origin

PNES Impact on the Patient

- Antiepileptic Drug therapy (90%)
  - Side effects
- Disability
  - Restrictions on driving
  - Restrictions on work
- Psychological/Social effects
- Cost of assessment and treatment

Psychogenic Seizures (PNES) Frequency

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>PNES Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>King et al</td>
<td>1982</td>
<td>20%</td>
</tr>
<tr>
<td>Bowman et al</td>
<td>1996</td>
<td>33%</td>
</tr>
<tr>
<td>Martin et al</td>
<td>2003</td>
<td>32%</td>
</tr>
<tr>
<td>Benbadis et al</td>
<td>2004</td>
<td>30%</td>
</tr>
<tr>
<td>Salinsky et al</td>
<td>2011</td>
<td>26%</td>
</tr>
</tbody>
</table>

King DW et al, Neurology, 1982
Bowman ES, Markand ON Am J Psychiatry, 1996
Martin R et al, Neurology, 2003
Benbadis SR et al, Epilepsia, 2004
Salinsky MC, Neurology, 2011

Post-traumatic Epilepsy

- Population-based studies
  - Chart review, administrative databases
  - Seizures assumed to be epileptic
  - Few cases confirmed by monitoring

Post-traumatic seizures

Traumatic Brain Injury

PNES

2. Pugh MJ, Ann Neurol, 78-800.001; 2012
Head Injury and Psychogenic Seizures (PNES)

<table>
<thead>
<tr>
<th>Author</th>
<th>Type</th>
<th>% of PNES patients</th>
<th>Percent with documented head injury</th>
<th>Mean age (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barry et al, Epilepsia 1998</td>
<td>Retrospective; video-EEG monitoring</td>
<td>157</td>
<td>24%</td>
<td>34 (15-56)</td>
</tr>
<tr>
<td>Westbrook et al, Epilepsia 1998</td>
<td>Retrospective; video-EEG monitoring</td>
<td>102</td>
<td>32%</td>
<td>34 (17-57)</td>
</tr>
</tbody>
</table>

PNES Severity of Head Injury

![Barry et al, Westbrook et al, Annegars et al]

TBI Severity and Seizures U.S. Veterans

- **Hx of mild TBI as cause of seizures**
  - >82% with PNES

- **Hx of severe TBI as cause of seizures**
  - >90% with epilepsy

Seizures after moderate-severe TBI

- Result of video-EEG monitoring (n=127)
  - Psychogenic: 18%
  - Epileptic: 27%
  - Nondiagnostic: 55%

TBI and PNES U.S. Veterans

- ** ↑ seizure risk (post-traumatic)**
  - >50% with severe military TBI\(^1\)
  - >35-65% in mild military TBI\(^2,3\)
  - Associated with PNES
  - Associated with PNES in civilian studies\(^4\)
  - 33-65% in mild military TBI\(^2,3\)
  - Less in moderate-severe TBI\(^6\)

Discharge Diagnoses

- Veterans: 16% PNES, 25% Mixed, 12% NES Other, 41% Nondiagnostic
  - Epilepsy: 41%, PNES: 16%

- Civilians: 25% PNES, 27% Mixed, 4% NES Other, 38% Nondiagnostic
  - Epilepsy: 40%, PNES: 25%
TBI as Cause of PNES

**Civilians vs. Veterans**

<table>
<thead>
<tr>
<th>Event</th>
<th>Civilians</th>
<th>Veterans</th>
</tr>
</thead>
<tbody>
<tr>
<td>% with proposed TBI etiology</td>
<td>56%</td>
<td>26%</td>
</tr>
</tbody>
</table>

For veterans - 50% of TBIs were military TBIs

Veterans with PNES vs. ES

**Mental Health Evaluations**

<table>
<thead>
<tr>
<th></th>
<th>PNES</th>
<th>ES</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>68</td>
<td>54</td>
<td></td>
</tr>
<tr>
<td>Age at Admission</td>
<td>48.4</td>
<td>49.9</td>
<td>NS</td>
</tr>
<tr>
<td>Any Axis 1 Diagnosis (%)</td>
<td>77.9</td>
<td>66.7</td>
<td>NS</td>
</tr>
<tr>
<td>Number of Axis 1 Diagnoses</td>
<td>3 (0-8)</td>
<td>2 (0-6)</td>
<td><strong>0.01</strong></td>
</tr>
<tr>
<td>Any Axis 2 Diagnosis (%)</td>
<td>27.9</td>
<td>16.7</td>
<td>NS</td>
</tr>
</tbody>
</table>

Veterans with PNES vs. ES

**Multivariate Analysis**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTSD</td>
<td>5.7</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Szmuk et al, Epilepsy and Behavior; 2012

Veterans with PNES vs. ES

**Psychiatric Historical Variables**

- Total Axis I diagnoses
- Any Axis II diagnosis
- PTSD
- Duration of seizures
- Major depression
- Other depression
- Alcohol abuse
- Substance abuse
- Adjustment d/o
- Bipolar d/o
- Any Psychiatric Admit
- Number of Psychiatric Admits

TBI and Psychogenic Seizures

**Key Points**

1. **Traumatic Brain Injury + seizures ≠ epilepsy**
   - Some have PNES
2. **Mild TBI**
   - Strong association with PNES
   - Weak association with epilepsy
3. **PTSD is strongly associated with PNES**

Hoge et al, NEJM; 2008
Pietrzak et al, J Nerv Ment Dis; 2009

TBI and Psychogenic Seizures

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Pietrzak et al, J Nerv Ment Dis; 2009
Surgical Management of Post-Traumatic Epilepsy

Complexities-Adhesions and Multifocality

December 2, 2012

Jeffrey P. Blount MD
Division of Neurosurgery
University of Alabama at Birmingham
Children’s of Alabama

American Epilepsy Society | Annual Meeting

Learning Objectives

• Published surgical experience/outcomes in PTE is limited
• Inherent limitation-diffuse nature of injury in TBI unlikely to result in epilepsy of focal onset
• Invasive investigation of PTE often challenged/limited by adhesions/webs within areas of encephalomalacia
• Despite limitations limited evidence suggests effectiveness and promise of surgical intervention for PTE

Silent epidemic of head injury

• Traumatic Brain Injuries(TBI)-common
  – 1.2-1.7 million adult cases TBI/yr in EU/USA
  – 300K hospitalizations and 50K adult deaths/year
  – 475,000 children with TBI/yr in USA
  – Most common in young (males) and elderly
• Post traumatic epilepsy (PTE) frequent after TBI
  – 10-20% severe TBI patients develop PTE
  – TBI accts for 4% of all focal epilepsy and 5% of all epilepsy referred to specialized centers
  – Younger age and higher TBI severity increase risk

American Epilepsy Society | Annual Meeting 2012

Disclosure

No financial disclosures

American Epilepsy Society | Annual Meeting 2012

Risk factors for refractory seizures post head injury

• Early seizures
• Penetrating injury
• Depressed skull fracture
• Sub-dural hematoma

Only about 1/3rd of patients with PTE respond medically
100K severe TBI/year → 15000 develop PTE post TBI → ~5000 new cases of medically resistant PTE per year in US

What is appropriate role for surgery??

**Treatment of Epilepsy**

- Medical Treatment with anti-epileptic drugs (AEDs)- will control about 2/3rds of children with epilepsy
- If medical treatment ineffective:
  - Surgery offers real likelihood of improvement and/or cure
  - Surgical effectiveness continues to increase
  - Wide variety of surgical options means many different candidates for epilepsy surgery
- Surgery now represents a highly effective low risk treatment for many children with MRE...but...
- Surgical decision making dependent on extent of localization of where the epilepsy arises from...

**Challenges to surgical approach to PTE**

- Localization/ potential for multi-focality
  - Traumatic injury characteristically diffuse- less likely to impart focal region of epileptogenesis (?)
  - Rare to have single focal injury
- Scarring/adhesions
  - Regions of post traumatic arachnoid scar and adhesions impair ability to position subdural grid electrode arrays

**Localization in PTE**

- Closed head injury
  - Pathophysiology-diffuse delivery of massive energy (acceleration/deceleration or blast) to brain parenchyma
    - Contusions
    - Hemorrhages
    - Axonal shearing, edema and ischemia
- Penetrating head injury
  - Pathophysiology-blast cone of energy produces cicatrix in the cortex
Seizure localization and pathology following head injury in patients with uncontrolled epilepsy

David A. Marks, MD, Jong Eun, MD, Dustin D. Seevers, MD, and James D. Seevers, MD

1982-1992 at YNH-25 patients with PTE- studied localization/pathology MRI, neuropsych, EEG, 21/05 or EEG
17 patients-temporal- EARLY CHI associated with MTS and GOOD surgical outcome
8 patients- neocortical- did well if Radiographic lesion evident

“as a group seizure foci secondary to head trauma are difficult to localize accurately and this should deter surgical intervention”

ISAS (Ictal-Interictal SPECT Analysis by Statistical Parametric Mapping [SPM])

Arachnoid scarring/fibrosis

- Regions of encephalomalacia that appear vacant on scans actually filled with dense web like scar
- This dense scar diffusely adheres to pia/surface veins - makes passing subdural electrodes difficult/ perilous

MEG showing extensive dipole cluster along margin of post traumatic region of porencephaly. Resection rendered patient sfr free.

Scarring-video of difficulty opening dura here password
14 yr old female – penetrating bi-hemispheric (tree branch) injury-severe PTE; EEG diffuse with L predominance.
Hemispherectomy without improvement
Dense adhesions and avascular tissue found at surgery

Posttraumatic epilepsy: The endophenotypes of a human model of epileptogenesis

- Ramon Díaz-Arrastia,
- Mark A. Agostini,
- Christopher J. Maddox,
- Paul C. Van Ness

Departments of Neurology and Neurosurgery, University of Texas Southwestern Medical Center, Dallas, Texas, USA.

Figure 8: Pictograms assessing imaging (PTE) and neurology follow-up examination (NE) in epilepsy patients. (A) PTE brain imaging, (B) PTE neuropsychological evaluation. (C) PTE neurology evaluation. (D) PTE clinical evaluation.

**POSTTRAUMATIC EPILEPSY**

Long-term outcome of extratemporal resection in posttraumatic epilepsy

- Shlomo Halperin, M.D.,\footnote{At the University of California, San Francisco.}
- A. George Barsky, M.D.,\footnote{At the University of California, San Francisco.}
- John W. Miller, M.D., Ph.D.,\footnote{At the University of California, San Francisco.}
- Jeffrey G. Davis, M.D., Ph.D.,\footnote{At the University of California, San Francisco.}
- David O. Hebb, M.D.,\footnote{At the University of California, San Francisco.}
- Richard H. Christine, M.D., Ph.D.,\footnote{At the University of California, San Francisco.}
- George A. Oldfield, M.B., F.R.C.S.,\footnote{At the University of California, San Francisco.}

Department of Neurological Surgery and Neurology, University of Washington, Regional Epilepsy Center, Harborview Medical Center and University of Washington Medical Center, Seattle, Washington, and Department of Neurosurgery, Georgetown Medical Center, Denville, and Temple School of Medicine, Philadelphia, Pennsylvania.

- 21 patients/17 year interval with PTE.
- 6/21 seizure free (28%) AND 6 had <2 szrs/month.
- 5/24 had seizure reduction

Good or excellent outcomes in 83% 

British Journal of Neurosurgery, April 2015; 29(3): 324 – 330

Origins of Article

Characteristics and surgical outcomes for medial temporal post-traumatic epilepsy

P. Hartfield, R. Elsey, F. Pac, B. Smith & J.A. Outterhouse

Department of Neurosurgery, Radiology, Anesthesiology, Henry Ford Health System, Detroit, Michigan, USA

57 PTE patients over 10 year period reviewed.
30/57 had temporal lobe onset. Most common etiology: blunt trauma
19/30 Engel Class 1

Post traumatic TLE cases do as well surgically as non traumatic etiology temporal lobe cases

Ranalli and Limbrick et. al.

- Retrospective review at SLCH and CCH
- Medically refractory epilepsy = spontaneous recurrent chronic seizures despite optimal dosing of 2 or more anticonvulsants
- 17 patients (20 surgeries) for PTE 1993-2010
Surgery Types
- Lobectomy: 40%
- Hemispherotomy: 30%
- Callosotomy: 20%
- Vagus Nerve Stimulator: 10%

Engel Class
- Class IV
- Class III
- Class II
- Class I

Conclusions
- Surgery is of benefit in selected individuals with PTE
  - 45% had significant improvement in seizure outcomes (Engel I and II)
  - 65% had worthwhile improvement in seizure outcomes (Engel I - III)
- Corpus callosotomy is successful as a palliative procedure, achieving a “worthwhile” outcome in 75% of cases

Published Surgical Outcomes in PTE
- Hakimian: good or excellent outcomes in 83%
- Hartzfield: PTE temp lobe cases do as well as non-PTE temp lobe cases
- Jiang: 61% (11/18) treated surgically had good-excellent outcomes
- Lee: 2/2 with PTE Seizure free with VNS
- Rannalli and Limbrick: 45-65% seizure free; 75% improved with CCS

Conclude: preponderance of favorable outcome

Impact on Clinical Care and Practice
- Localization of PTE is difficult due to diffuse and widespread nature of injury
- Contemporary non-invasive functional imaging studies (MEG, IS) may contribute to localization
- Invasive electrode placement is more laborious, time consuming and probably associated with greater risk of surgical complications
- Promising results have been obtained with surgical treatment of PTE and should be considered for those patients demonstrating medical resistance to PTE
Post Traumatic Epilepsy: Conclusions and Algorithm
December 2, 2012
Joseph I. Sirven, MD
Professor and Chairman
Department of Neurology
Mayo Clinic Arizona
Phoenix, Arizona USA

Disclosure
Eisai, MAP, Vertex,
Upsher-Smith, Lundbeck,
UCB, Neupace, NIH

Learning Objectives
• To summarize the main points from this afternoon’s session
• To present an algorithm for management of Post-traumatic epilepsy

Flash Panel
• Increased risk of epilepsy is limited to moderate and severe civilian TBI which comprises 5% of all cases
• In people under age 35 years, TBI increases the risk for GTCS, CPS
• Risk Factors include: brain contusion, SDH, linear or depressed fracture, LOC > 24 hours, age over 65 years

Flash Panel
• Risk for epilepsy after civilian TBI is greatest in the first two years after TBI in most studies except for one study suggesting that severe TBI the risk persists for 10 years

Antiepileptogenesis
• New biomarkers of risk are promising: MRI techniques
  – Hippocampal changes
  – Interictal spike features, fMRI
• EEG
  – PHFOs Pathological high frequency oscillations
• AMT PET imaging
• No definitive genetic biomarkers
Debate

- Prophylactic AEDs reduced acute symptomatic seizures after severe TBI but not epilepsy
  - AEDs may prove useful in suppressing epileptogenesis

Imaging and EEG in Post-Traumatic Epilepsy

- EEG and MRI are important in the diagnosis of Post-traumatic epilepsy (PTE)
- Different techniques elucidate different lesion types
  - Lesion type
  - Provide data to identify those at risk for developing PTE
- May be important to identify candidates for therapeutic intervention

Post-Traumatic Epilepsy Treatment

- AEDs- mainstay of therapy
- Surgery
  - Best prognosis with a single lesion
  - Multifocal EEG has a worse prognosis
  - Role of multimodal assessment tools

Traumatic Brain Injury and Spells

- Traumatic brain injury and spells do not imply epilepsy
  - Some will have Psychogenic Nonepileptic Seizures (PNES)
- Mild or minimal TBI
  - Strong association with PNES
  - Weak association with epilepsy
- Post-trumatic stress disorder is associated with PNES