EPILEPSY CURRENTS

Epilepsy Benchmarks

Epilepsy Resources and Updates

2014 Epilepsy Benchmarks Area IV: Limit or Prevent Adverse Consequence of Seizures and Their Treatment Across The Lifespan

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Area IV Benchmarks focus on mechanistic understanding and prevention of epilepsy-related consequences. As such, these Benchmarks cover "epilepsy beyond the seizures," areas related to the neurodevelopment, mental health comorbidities, intellectual functioning, and general health of individuals with epilepsy, the short- and long-term effects of antiseizure treatments, and risks for epilepsy-related mortality. This area also covers unique issues of special populations with seizures, such as pregnant women, children, the elderly, and people with nonepileptic seizures.

Key Advances in Area IV

Consequences of Epilepsy

It is now well established that people with epilepsy (PWE) are affected not only by their disease but that seizures exert much broader consequences on their physical, mental, and social wellbeing. PubMed search using terms "epilepsy and quality of life" and "epilepsy and comorbid conditions" yielded approximately 700 publications between 2013 and 2016. This underscores recent scientific interest in these challenging issues faced by PWE and their families and caregivers. Much work remains to be done to understand risk factors and achieve mechanistic understanding of epilepsy-related comorbidities.

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Epilepsy and Health-Related Quality of Life (QOL)

Epilepsy makes up a quarter of the global disability-adjusted life years for neurologic conditions (1). Systematic survey of 250 epilepsy patients showed that young age, lack of seizure freedom, epilepsy severity, and anxiety are statistically significant predictors of disability, with age and epilepsy severity accounting for 25% and 30% of these determinants, respectively (1). While some concerns seem common to all PWE, there are also syndrome or epilepsy type-specific issues as documented by the recent international collaborative study that analyzed the burden of idiopathic generalized epilepsy (2). Treatment-related adverse effects are also an important determinant of the health-related QOL (3). One must also consider the impact of epilepsy on patients' social network. Parents of children with epilepsy demonstrate diminished health related QOL, and mothers are especially vulnerable to anxiety disorder (4).

Epilepsy and Risk of Comorbidities

There is growing evidence that the consequences of chronic epilepsy extend beyond the direct effects of seizures. An example is a recent statewide population analysis that included large minority and socioeconomically disadvantaged groups and compared comorbidities in over 64,000 PWE with almost 122,000 patients with migraine (PWM), and nearly 90,000 non-neurological/otherwise healthy controls (5). The absolute risk increase for any somatic and psychiatric/neurodevelopmental comorbidity was 94.3% for PWE compared with 58.8% for PWM (5).

Neurodevelopment and Intellectual Disability

Experimental and human research indicates that epileptic seizures exert adverse effects on cognition and behavior, but there is also evidence that epilepsy may represent a surrogate marker of a more broadly distributed intellectual problem (6–9). For example, 24% of 1133 children with intellectual disability carried a coexisting diagnosis of epilepsy in a multicenter population-based study (10). Similarly, recent population analysis showed an 18-fold increase in autism spectrum disorder (ASD), 16-fold increase in cognitive dysfunction, and 27-fold increase in intellectual disability (ID) in PWE compared with patients with migraine (5). In the past few years, the combined phenotypes of epilepsy, ASD, and ID were linked to mutations in genes involved in synaptic transmission and neuronal plasticity, such as the *SHANK3* (11) and *PCDH19* genes (12), the *NMDA* receptor gene family (13), mTOR pathway proteins (14), and others (see also Area I report). It is also well recognized that malformations of cortical development (MCD) are often associated with pharmacoresistant epilepsy, autism, and ID (15). There are now more than 30 genes principally linked to MCD and the complex epileptic and intellectual phenotypes (15) and their individual and combined roles in the temporal and spatial regulation of neurodevelopment will require further study. Even patients with nonlesional and traditionally considered "benign" epilepsies are now being recognized as being at risk for neurodevelopmental issues. Attention deficit disorder or problems in language and executive functions are frequently seen in childhood absence, rolandic, and juvenile myoclonic epilepsies (16–18). There is also evidence of a familial aggregation of these disabilities as illustrated by the reading disability prevalent in 42% of probands with Rolandic epilepsy and 22% of their siblings (19) These studies highlight patient populations at risk for relatively mild but important cognitive impairments that, if addressed early, may improve the child's psychosocial integration and QOL.

Issues related to memory are frequently noted at all stages of life in PWE. Retrospective analysis of 70 adults who underwent temporal lobectomy showed that uncontrolled seizures were associated with cognitive decline (20), while memory functions of post-surgical patients with fully controlled epilepsy remained stable over a period of 5 years (20). Interestingly, cognitive issues are a common characteristic in epilepsy as well as in mild cognitive impairment. Amyloid plaques, the hallmark in Alzheimer's dementia (AD), were identified in 10% of resected temporal lobe specimens from operated temporal lobe epilepsy (TLE) patients who did not exhibit dementia by neuropsychological tests, and the age-related incidence of plaques in TLE patients was significantly higher compared with age-matched nonepileptic controls (21). Conversely, patients with familial AD type demonstrate increased frequency of clinical seizures and several AD animal models display combined phenotype of cognitive impairment and epileptic seizures (21). Interdisciplinary human and animal research will be important to decipher molecular mechanisms underlying vulnerability to cognitive decline in adult PWE.

Animal models have been instrumental in demonstrating the detrimental effect of chronic seizures on cognitive function. Genetic absence epilepsy rats are prone to increased anxiety behaviors, diminished exploratory activity, and depressive-like symptoms (22, 23). The rat model with transient focal prefrontal interictal spiking induced by bicucculine exhibits lasting and marked inattentiveness and impaired sociability that improved with a timely administration of adrenocorticotropin hormone (24, 25). These results indicate that even transient impairment in GABAergic signaling in the developing brain can lead to enduring deleterious behavioral effects that may be prevented with early detection of the epileptiform activity and timely intervention.

Epilepsy and Mental Health Disorders (MHD)

There is approximately 35% lifetime prevalence of psychiatric comorbidities among PWE (26). Mood and anxiety disorders are the most common and they are the strongest independent variable predicting increased risk of suicide, premature death, and poor QOL (27). Similarly to cognitive dysfunction, there is a complex bidirectional relationship between epilepsy and MHD; PWE are at increased risk for developing MHD, while patients with "primary" psychiatric disorders are predisposed to developing epilepsy (28). Major depressive episode and bipolar or anxiety disorders are associated with and 2.5-fold and 2.7 increased risk for developing epilepsy, respectively (29) Similarly, children with attention deficit disorder of the inattentive type are 3.5-fold more likely to develop epilepsy (28). The predisposition to epilepsy in patients with MHD does not seem facilitated by the exposure to psychotropic drugs as evidenced by higher incidence of seizures in patients with major depressive disorder (MDD) randomized to placebo than in those taking selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs) (28). Human research of mood disorders and epilepsy indicates convergence along disturbances in serotonergic transmission and opioid signaling, dysregulation in the hypothalamic-pituitary-adrenal axis, and activation of inflammatory pathways (30). Experimental animal studies have paralleled these observations and more research is needed to further delineate the candidate pathways and the specific mechanisms that lead to comorbid MHD with epilepsy.

Other Epilepsy-Related Comorbidities

Migraine is the most common neurological comorbidity of epilepsy with an estimated prevalence of 20 to 40 percent (27). Genome-wide association studies of MH patients have identified susceptibility gene variants clustering along pathways with known or suspected role in epilepsy, and mutations in several epilepsy genes (*CACNA1A*, *SCN1A*, and *ATP1A2*) are also associated with genetic migraine (31). Notably, migraine, depression, and epilepsy are common comorbid conditions and the presence of any one of these disorders increases risk for the development of the others (27, 32) Further research of the available patient cohorts and cross disciplinary analysis of the many genetic animal models offers interesting opportunities for improved understanding of the individual disorders and their oft detected coexistence.

PWE are also at 4-fold increased risk for stroke (5) and face 3-fold increase in the risk for venous thromboembolism (33). More research will be necessary to define factors specific to PWE predisposing to cerebrovascular and cardiovascular disease risk.

Psychogenic Nonepileptic Seizures (PNES)

The International League Against Epilepsy (ILAE) NES Task Force recently published diagnostic levels of certainty for PNES with the intent to provide clinical guide in the evaluation of these patients (34). New research on automated differentiation between epileptic and nonepileptic seizures using surface electromyography (EMG) is also showing great promise, with an overall positive predictive value of 96% (35). A multicenter pilot randomized clinical trial for PNES in the United States showed significant reduction in PNES and improvement in comorbidities and functioning in the two cognitive behavioral informed psychotherapy arms (30). In the United Kingdom, a new multicenter randomized controlled trial of cognitive behavioral therapy (CBT) versus standard medical care for PNES (36) has the potential to add significantly to our growing understanding of the effect of psychotherapy. A recently published study of group psychoeducation for PNES demonstrated improvement in the Work and Social Adjustment Scale scores at 3 and 6 months after Epilepsy Monitoring Unit discharge (37). These avenues of PNES treatment research are building the foundations for evidence-based treatment tools (38).

Risk factors for PNES are being delineated. Veterans presenting with poorly controlled seizures and a history of traumatic brain injury (TBI) are diagnosed with epileptic seizures or with PNES at similar rates. A diagnosis of PNES seems to predominate when the antecedent TBI was mild and when post-traumatic stress disorder (PTSD) is also present (39). Compared with their siblings, children with PNES have more lifetime comorbid medical, neurological, and psychiatric problems, use more medications and intensive medical services, have higher anxiety sensitivity, practice solitary emotional coping, and experience more lifetime adversities (39). Cluster analysis of adults with PNES revealed two categories of emotional processing: a group with difficulties with most aspects of emotional regulation, and a second group with a distinct psychological profile of high somatization but normal emotional processing. Further research is needed to evaluate whether PNES are due to emotional dysregulation (as has been the traditional theory) or, a result of fundamental problems with perceptual and behavioral control (40).

Sex-Specific Issues in Epilepsy

Clinical and experimental research has shown that chronic epilepsy and its medical treatment frequently affect reproductive health in both women and men (41). In women, epilepsy affects sexual development, menstrual cycle, and pregnancy outcome among other issues. Conversely, the hormonal milieu impacts seizure activity. Women with catamenial epilepsy have fewer seizures in pregnancy compared with women whose seizures are not associated with the menstrual cycle (42, 43), thus supporting prior basic and clinical science that reproductive sex steroid hormones influence seizure susceptibility. Seizures and even epileptiform discharges can disrupt normal pulsatile secretions of the hypothalamic-pituitary-gonadal axis, a mechanism implicated in sexual and reproductive complications of chronic epilepsy in men and women (41). Women with epilepsy are also at increased risk for peripartum depression and anxiety compared with women without epilepsy (44). Men with epilepsy are more likely to report loss of libido, erectile dysfunction, and sexual dissatisfaction, and these clinical complaints tend to correlate with detectable hormonal imbalance (41, 45). Adverse effects of epilepsy or antiseizure therapy on sleep quality and mood can further impair reproductive health (41).

With respect to the treatment, antiseizure medications and psychoactive therapy aimed at the comorbid mood disorder can also adversely affect sexual functions (46, 47). Additionally, there are unique consequences of antiseizure medication use in pregnant women and their children (48). Prospective worldwide registries find that valproate is consistently associated with increased rates of major congenital malformations as compared to other commonly used antiepileptic drugs (49) and the National Birth Defects Prevention Study (NBDPS) has corroborated these findings; the analysis of the 18,631 cases with birth defects and 6807 nonmalformed controls showed that prenatal valproate exposure was associated with odds ratio of 9.7 (95% confidence interval [CI] 3.4–27.5) for neural tube defects, 4.4 (95% CI 1.6–12.2) for oral clefts, 2.0 (95% CI 0.78–5.3), and 2.4 (95% CI 0.62–9) for hypospadias. Prenatal exposure to carbamazepine showed a 5-fold increase risk for neural tube defects (50). The health risk associated with exposure to some of the newer antiepileptic drugs is less well defined but will be important to address because preliminary data show that topiramate and zonisamide may increase risk for lower birth weight (51). Additionally, exposure to antiseizure medications during the fetal and early postnatal period poses risk for cognitive, behavioral, and emotional development of a child (52–55). Maternal intake of valproate at any dose poses risk for impaired verbal IQ of the child and at doses over 800 mg daily, it increases the risk for autistic spectrum disorder and intellectual disabilities (48, 56, 57). While timely folate supplementation has long been known to reduce neural tube defects, there is a dearth of other therapeutic interventions that would neutralize the developmental risk rendered by antiseizure therapy.

Consequences of Antiseizure Treatments

All therapeutic interventions aimed to control seizures (medications, surgery, dietary therapies, or neurostimulation) have side effects. For example, perampanel, a noncompetitive AMPA-receptor antagonist, is the newest antiseizure drug. However, behavioral changes and sedation often limit its use (58). During the past 4 years, new work focused on medication effects showed that in children that became seizure free following epilepsy surgery, reduction, and early withdrawal of antiseizure medications led to significant improvement and gain in postoperative intellectual quotient, independent of other determinants of cognitive outcome (59).

There have been several novel surgical approaches introduced to PWE in the past 4 years. They include stereotactic laser ablation (SLA), responsive neurostimulation (Neuropace), and anterior nucleus of the thalamus stimulation. Pilot studies point to SLA being efficacious and it seems to be associated with fewer cognitive consequences than traditional open resection approaches (60), arguing that many of the cognitive deficits associated with resective surgery reflect surgically imposed "collateral" damage to the tissue adjacent to the ictal focus. Responsive neurostimulation (RNS) has been shown to both reduce seizure frequency and improve quality of life

in patients with treatment refractory partial onset epileptic seizures (61–63). Moreover, at 2 years, there was a small but significant improvement in naming in patients with neocortical seizure onset, as well as improvement in learning in patients with seizure onset from the mesial temporal structures (64). The "Stimulation of the Anterior Nucleus of the Thalamus for Epilepsy" (SANTE) trial has shown efficacy in reducing seizure burden in patients with medically intractable epilepsy and gains were reported in QOL along with an improvement in several neuropsychological measures (65). The infrequent but most common serious adverse event in RNS and SANTE trials was infections at the implant site (46, 65). While the initial data on QOL and adverse events of these alternative surgical interventions is encouraging, ongoing systematic, and standardized evaluation of large patient cohorts will be important for more definite assessment of their use in clinical practice.

Epilepsy-Related Mortality

Sudden unexpected death in epilepsy (SUDEP) is a serious public health issue as it is second only to stroke in the years of productive life lost (66). Epilepsy patients with poor health and low income appear to be at nearly twice the risk for premature death when compared with the general Medicaid population (67). In the past 4 years, there has been much progress in the mechanistic understanding of SUDEP; the MORTEMUS study (68) showed a consistent pattern of lethal cardiorespiratory dysfunction following a secondary generalized tonic-clinic seizure (GTCS). Pilot imaging analysis in two SUDEP cases and 30 patients with TLE followed on the clinical and experimental indices of cardioautonomic dysfunction and found that TLE patients had volume loss in the dorsal mesencephalon but the SUDEP cases had severe and more extensive volume loss in this region (69). By contrast, increased gray matter volumes (GMV) in the right anterior hippocampus/amygdala and parahippocampus were found in SUDEP cases and people at high SUDEP risk compared with living PWE (47). The volume of posterior thalamic GMV, an area mediating oxygen regulation, was reduced in these patients. These studies, if confirmed, will make possible premortem risk identification with imaging in patients with epilepsy.

Detailed genomic analysis in an index SUDEP case affected by Dravet syndrome uncovered an oligogenic influence of several genes involved in the neurocardio-respiratory pathways, thus corroborating prior experimental and human research (70). Individually increased polygenic burden of rare deleterious variants was subsequently identified in a case series of 18 SUDEP individuals (71). Most recently, the rare phenotype of alternating hemiplegia in childhood was found to be associated with impaired cardiac repolarization reserve as manifested by often ephemeral abnormalities on the electrocardiogram (72). This study has thus identified a novel candidate patient group at risk for SUDEP and the associated gene, *ATP1A3* has been added to the growing list of candidate SUDEP molecules. Research in animal models has led to further elucidation of the role of the monoamine pathways in respiration and arousal (73, 74) as well as to the discovery of a novel candidate SUDEP mechanism, brainstem spreading depolarization (SD) (75). Topical brainstem application of 4-aminopyridine in two SUDEP prone genetic mouse models induced seizures that led to a slow, irreversible depolarization of the brainstem subsequent to EEG suppression, apnea, bradycardia, and asystole, as occurs in monitored human SUDEP. This important discovery offers novel mechanisms and a biological pathway toward cardiorespiratory failure frequently observed in epilepsy-related sudden death. Development of technologies such as CRISPR and TALEN is enabling much faster generation of mouse models that enable study of individualized gene mutations as exemplified in the *Scn8a* (N1768D) mutant mice that confirmed the causality of this variant in human SUDEP (76). Similarly, studies of induced pluripotent stem cell–derived neurons in Dravet syndrome patients offer novel, personalized mechanistic analysis and pharmacogenomics studies in epilepsy and in SUDEP (77, 78).

Looking Forward: Challenges and Opportunities

There has been an increased attention to epilepsy-related consequences and comorbidities. Yet, challenges and opportunities in Area IV remain. It is becoming evident that epilepsy, migraine, mental health disorders, developmental, and cognitive issues converge along common pathways because all these conditions have shared predisposition. Understanding the expression and severity of epilepsy comorbidities and related therapies offers novel research opportunities. Broader usage of common data elements in the ascertainment and evaluation of patients will help maximize use of data across research studies. Randomized controlled trials (RCTs) are the gold standard in the evaluation of a novel therapy. However, evaluation of surgical approaches and interventions in pregnant women with epilepsy poses serious practical or ethical barriers to RCTs and standardized evaluation and reporting of observational data may be the best available alternative. The use of common care pathways and standardized collection of prespecified outcome measures are needed to enable rapid, affordable development of high-quality evidence in many critical areas of patient care. These data would be valuable to researchers, regulators, and payors, and ultimately and most importantly, to patients. Similarly, an initiative to standardize behavioral and EEG profiling in animal models of human epilepsy would be helpful for the purpose of comparative analyses and to increase the translational use of the model systems. Standard behavioral assessments and correlated EEG abnormalities could better guide development and implementation of therapeutic interventions. The Translational Taskforce partnership among the ILAE, AES, and NINDS (see also Area II report) is underway to address these issues.

Large-scale intra- and interdisciplinary collaborations are becoming increasingly important for progress toward understanding the mechanisms and consequences of seizures, epilepsy-related comorbidities, and outcomes and in defining the risk/benefit ratio of antiseizure therapy. This is especially true in the areas of PNES, mental health issues, neurological comorbidities, and epilepsy-related mortality where close interaction among neurologists, psychiatrists, and associated health care professionals is critical to success.

The need continues for population-based studies, clinical, and experimental research in order to further define mechanisms and the short- and long-term risks of a broad range of existing and newly emerging antiseizure medica-

tions on the developing fetus and newborn child. There is also very little understanding about the effect of common comorbid conditions and their treatments on fetal and neonatal development. This area represents an important research opportunity and multispeciality collaborations will be crucial.

The most recent progress in the field of epilepsy-related mortality has unquestionably been in understanding the incidence and potential mechanisms of SUDEP. Several opportunities for large-scale collaboration, such as coordinated research programs offered by Citizens United for Research in Epilepsy, the Epilepsy Foundation, Centers for Disease Control, and the NINDS have contributed to these advances. In the near term, it will be important to test the mechanistic hypotheses emerging from research on SUDEP animal models in human studies, and to distill the many currently emerging clinical, biochemical, imaging, genetic, and molecular markers into a premortem SUDEP risk index. Additional research into other underlying (and preventable) causes of epilepsy-related mortality, such as suicide, remains a need. Prognosis and mortality risk in the era of modern antiepileptic drug therapy is a relative unknown.

Epilepsy continues to demonstrate a complex interplay of genetic and environmental factors. Seizures, treatments, and associated complications impact patients from the prenatal period until old age. It will be important to understand QOL issues related to epilepsy subtypes so that personalized medicine does not stop at diagnosis. Identifying adverse effects of antiseizure treatments in specific populations at different developmental stages is a needed precursor to understanding their causes and finding biomarkers of risk. Epilepsy imaging research has brought forth candidate regions of interest in epilepsies, cognitive and mental health disorders, as well as in sudden death in epilepsy with the aim to serve as clinically useful specific biomarkers. Clinical replication supported by mechanistic research will be important before this goal can be realized. Advances in symptomatic and preventative care will require multidisciplinary collaboration, engagement of patients and their families, and the development of newer technologies and research approaches.

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