Current Controversies in Epilepsy: Brain Injury and Cognitive Consequences

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Abstract  The onset of seizures may follow head injury or may be a symptom related to any number of medical conditions. At a session held during the 2012 Annual Meeting of the American Academy of Neurology, experts discussed surgical interventions that may benefit patients who experience seizures, cognitive problems related to seizure activity, links between autism and epilepsy, and current knowledge concerning the occurrence of epilepsy following brain injury.

Epilepsy, one of the most common neurologic conditions, is associated with significant morbidity and mortality. It affects more than 70 million people around the world.1 At a symposium held during the 2012 Annual Meeting of the American Academy of Neurology (AAN), experts reviewed current controversies regarding epilepsy, its comorbidities, and its treatment. Among topics covered were optimal therapeutic strategies for refractory epilepsy, the natural history of cognitive dysfunction in epilepsy, and associations between epilepsy and other disorders (eg, autism) or trauma (eg, concussions, head injuries). The session was chaired by David Labiner, MD, Head of the Department of Neurology and Director of the Arizona Comprehensive Epilepsy Program at the University of Arizona in Tucson.

Surgery vs Radiosurgery: Seizure Freedom and Cognitive Cost

Based on a presentation by Samuel Wiebe, MD, MSc, FRCP, Professor of Clinical Neurosciences; Head, Division of Neurology; and Director of Clinical Research, Hotchkiss Brain Institute, University of Calgary, Calgary, Alberta, Canada

Mesial temporal lobe epilepsy (MTLE), a syndrome that typically occurs during adolescence, is characterized by specific complex partial seizures referred to as “limbic seizures.” Many affected patients have not received benefit from several medications, and their seizures are considered refractory, making this condition the most common of the drug-resistant, surgically treatable epilepsies. The most prevalent pathologic feature of MTLE is hippocampal sclerosis, which was described as early as the 1800s. Removal of atrophied hippocampi was first popularized in the 1950s. Since then, localized surgical resection has progressed as more information about the focal pathology of the hippocampus has been published.

Investigators also have reported important evidence about seizure-onset zones outside the hippocampus. At least 56% of MTLE seizures occur beyond this region (eg, the amygdala, parahippocampus, and entorhinal cortex).2 MTLE is a network disorder. Optimal resective surgical strategies need to take into account that important network components may reside in the extrahippocampal medial temporal cortex in some patients.

Results of a randomized clinical trial3 and guidelines published by the AAN4 have established anterior temporal lobe resection (ATLR) as the effective procedure of choice for patients with drug-resistant MTLE. More recently, alternative techniques and approaches have been developed for more selective resection or ablation. Selective amygdalohippocampectomy (SAH) and radiosurgery have gained popularity among neurologists and neurosurgeons hoping to reduce the risk of cognitive decline but maintain the rates of seizure freedom. The relative outcomes of seizure freedom and rates of cognitive decline related to these three interventions are subjects of great interest.

Examining Cognitive Function

When measuring cognitive decline in patients who undergo temporal lobe resections/ablations, the different dimensions of memory function must be considered. The four main categories of memory that may be impaired are episodic, semantic, procedural, and working memory. The temporal lobe primarily is involved with semantic and episodic memory.5 Because cognitive decline varies between patients, measures that reliably show changes in specific memory domains tests must be used, and studies that use gross measures with grouped outcome data must be discounted.6

In ATLR, outcomes are well established; about 70% of patients remain free
of seizures after 1–5 years of follow-up, and about 60% remain seizure-free thereafter. A recent meta-analysis examined cognitive function after ATLR. The investigators found intelligence quotient (IQ) declines in 8%–16% of patients and gains in 13%–18% for combined left and right temporal lobectomy groups; they also noted verbal IQ gains in 11%–12% of patients and losses in 11%–18% of all temporal lobectomy patients.

However, another systematic review of long-term (> 5 years) outcomes found that the IQ of patients who underwent ATLR generally was unchanged in the long term. Reliable declines in word-finding ability occurred in 39% of patients after dominant ATLR. In terms of quality of life (QOL), over one half of patients achieved freedom from seizures and had improved QOL whether or not they experienced significant memory loss. Seizure outcome seemed to be more important to these patients' QOL than was verbal memory loss.

The results of numerous cohort studies have shown that SAH and ATLR produce similar rates of seizure freedom; however, these findings have not been shown in randomized, controlled trials. Patients who undergo SAH have cognitive and memory declines similar to those of individuals who undergo ATLR. However, in a meta-analysis, the results of 15 of 21 studies (71%) suggested that cognitive outcome following SAH may be better than that noted after ATLR.

Radiosurgery involves the firing of targeted radiation beams to a particular area, resulting in radionecrosis and functional ablation. Patients tend to achieve freedom from seizures if they are treated with an adequate radiation dose (> 20 Gy). Further, patients tend to experience delayed adverse effects due to the edema and necrosis that occur about 10–12 months after the exposure. Given the limited number of radiosurgery studies reported, cognitive outcomes after this procedure are not well known. However, some early evidence suggests that up to one third of patients who have undergone radiosurgery experience cognitive decline.

No randomized clinical trials have compared ATLR, SAH, and radiosurgery in MTLE patients, and an optimal therapeutic strategy still is unclear. Similar freedom from seizures (~ 70%) has been noted following ATLR and SAH; radiosurgical results with certain radiation levels have been competitive. As noted above, indirect evidence has suggested that cognitive outcomes are better after SAH than following ATLR. Cognitive outcomes following radiosurgery have not been established.

**COGNITIVE DYSFUNCTION AND ITS COURSE IN EPILEPSY: IS IT PROGRESSIVE?**

Based on a presentation by Bruce P. Hermann, PhD, Professor of Neurology, and Director, Charles Matthews Neuropsychology Laboratory, University of Wisconsin School of Medicine and Public Health, Madison

The cognitive effects of epilepsy over a lifetime are well known, but the relative contributions of prior neurodevelopmental factors and exact trajectory later in life are still conjectural. Two fundamental questions have yet to be fully answered. First, what is the time course of changes in cognition in people with epilepsy over their lifetimes? Second, how do neurodevelopmental factors contribute to cognitive impairment?

**The Course of Epilepsy**

Many studies have examined long-term cognitive outcomes in patients with childhood-onset epilepsy. However, many of these studies have been cross-sectional and have had inherent problems with assessing disease progression. Far fewer studies have included appropriate test-retest protocols in the same cohort over time. In a survey of longitudinal cognitive outcomes in adults and children with epilepsy, Dodrill showed evidence of a decline in cognitive function over time that was more obvious in children than in older patients. Dodrill also demonstrated that the decline affected multiple cognitive domains, although the data were presented in a singular group average.

The results of subsequent studies suggest the existence of patient subgroups with different courses of impairment (mildly impaired, memory impaired, and memory plus executive impairment). These phenotypes could be predicted by clinical epilepsy factors that included seizure frequency and the use of multiple antiepileptic drugs.

**Neurodevelopment and Cognitive Impairment**

Patients who have more severe epilepsy have worse outcomes, such as lower intellectual ability and educational difficulties. Predictors of cognitive impairment such as polytherapy, seizure frequency, and age of onset have been fairly consistent across studies. But how do children get to this point? To detect clues, several studies included a baseline assessment at diagnosis and followed patients for a prolonged period to study potential influences of antecedent neurodevelopmental problems and the long-term effects of epilepsy in these patients. This research resulted in evidence demonstrating that these patients had significantly more academic problems prior to their first seizure.

Another study that had more detailed cognitive dimensions and included patients with different epilepsy syndromes showed patterns of cognitive dysfunction, even in patients with more “benign” syndromes such as benign childhood epilepsy with centrotemporal spikes (BECTS).

Comorbidities observed before the onset of epilepsy include psychiatric manifestations such as major depression (45%), behavioral issues such as attention deficit hyperactivity disorder (ADHD), academic problems (16% vs 4% among control subjects), and cognitive difficulties. Use of quantitative MRI (qMRI) performed at the time of the diagnosis of epilepsy has provided emerging radiologic evidence of these potential influences.

Thus, differences in cognitive function and/or physiologic structures as found using qMRI provide important clues about epilepsy. In addition, evidence that antecedent neurodevelopmental factors contribute to these consequences also exists.

**Later Status and Trajectory**

One case-control study of long-term outcomes in patients with adolescent-onset temporal lobe epilepsy (TLE) dem-
onstrated dysfunction in regions beyond this area of the brain. In addition, bilateral dysfunction has been noted in patients with unilateral TLE.\textsuperscript{19}

Lin et al\textsuperscript{20} showed radiologic evidence of cortical thinning in extratemporal and bilateral areas of patients with unilateral TLE. In one study, they divided a large cohort of TLE patients into three subgroups according to severity of cognitive decline to find an anatomic correlation. The investigators noted a trend toward increased cortical thinning over the groups.

But do the cognitive effects progress? Approximately 20\%–25\% of patients with TLE have progressive epilepsy or experience worsening of their symptoms with time. A 4-year prospective study of cognitive ability showed that TLE patients had a decreased test-retest improvement effect when compared with controls.\textsuperscript{15} In particular, this subgroup had problems with confrontational naming, verbal memory, and psychomotor speed.

In summary, a substrate antecedent to the onset of epilepsy apparently contributes to cognitive decline. In addition, subsequent neurodevelopmental effects contribute to cognitive difficulties, and a chronicity of these effects has been documented in a patient subgroup.

\textbf{EPILEPSY AND AUTISM}

Based on a presentation by Deborah Hirtz, MD, FAAN, Program Director, Clinical Trials and Studies, Division of Extramural Research, National Institutes of Health/National Institute of Neurological Disorders and Stroke, Bethesda, Maryland

Autism was first described by Kanner\textsuperscript{21} and Asperger\textsuperscript{22} in the 1940s. Once considered a rare condition, autism previously was ascribed to schizophrenia and “poor mothering.” We now know it is a common biologic disorder that is being increasingly recognized and is represented by a spectrum of phenotypes.

The latest data from the Centers for Disease Control and Prevention (2008) show that 1 in 88 children has an autism spectrum disorder (ASD).\textsuperscript{23} Recently, the media have covered the rapid increase in the number of children with autism who have needed specialized medical and educational services.

The diagnosis of autistic disorder requires that patients meet the following \textit{DSM-IV} (\textit{Diagnostic and Statistical Manual of Mental Disorders, 4\textsuperscript{th} Edition}) criteria: qualitative impairment in (1) social interaction and (2) communication and (3) restricted repetitive and stereotyped patterns of behavior or activities.\textsuperscript{14} Approximately four times more boys than girls are diagnosed with autism.

Asperger’s disorder has been acknowledged to be a separate condition from autism in the \textit{DSM-IV}, but there are few studies to support this delineation. Childhood disintegrative disorder is rare and associated with global regression. The typical age at diagnosis is about 2–3 years for autistic disorder and 5–6 years for Asperger’s disorder.

Proposed changes for the new 5\textsuperscript{th} edition of the \textit{DSM} include a category known as ASD, which is based on only two criteria: (1) qualitative impairment in social interactions/communications and (2) repetitive behavior/fixated interests.

At-risk groups for having autism include premature infants and children who have siblings with autism, genetic disorders, or epilepsy.

\textbf{Coincidental Prevalences?}

The reported rate of epilepsy among children with autism varies from 5\% to 46\%, with a higher incidence seen among individuals with an intellectual disability. In a meta-analysis of children with autism and epilepsy, the pooled prevalence was 21.4\%.\textsuperscript{13} Seizure onset peaks both at an early age (<5 years) and during adolescence.

Many controversies surround the prevalence of autism among those with epilepsy. Children who have seizures early in life, symptomatic seizures, and infantile spasms are at highest risk of autism. When the true rate of autism in patients with epilepsy is assessed, however, referral bias is an important confounder. In a population-based study with prospective and long-term follow-up, 5\% of individuals with epilepsy had “primary” autism.\textsuperscript{26} Among those with epilepsy, autism is more common in patients with intellectual disability and in those diagnosed with epilepsy during the first year of life, possibly due to the high prevalence of West syndrome and infantile spasms and their association with ASD.\textsuperscript{25} Overall, 14\% of patients with infantile spasms have ASD.\textsuperscript{27}

Dravet syndrome is a severe epileptic encephalopathy that initially appears during the first year of life and is associated with multiple seizure types and refractory cognitive decline. One cohort of 37 children with Dravet syndrome included 9 patients with autism.\textsuperscript{28}

Landau-Kleffner syndrome (LKS), a rare but severe focal epilepsy, is characterized by a rapid decline in language function, which may result directly from seizures and is not a “primary” autism. However, developmental regression occurs in up to one third of patients with autism, usually about 18–24 months after its onset.\textsuperscript{29}

\textbf{Neurologic Testing and Autism}

Epileptiform activity in the absence of seizures has been reported. However, no population-based studies using electroencephalography (EEG) have been done in patients with autism.\textsuperscript{30} In one study, about 60\% of patients had epileptiform discharges during sleep.\textsuperscript{31} No guidelines currently recommend routine EEG testing in patients with autism.\textsuperscript{32}

\textbf{Genetics}

Numerous genes have been linked to autism and epilepsy. It is possible that commonly affected developmental pathways in synaptic plasticity are related to common genetic variation. Certain genetic defects could result in molecular derangements in ion channels and subsequently enhance neuronal excitation and inhibition. These same genetic defects...
seizures among more than 4,000 patients who experienced trauma was 1.5 after a mild TBI, 2.9 after a moderate TBI, and 17.0 after a severe TBI. A similar study at the Southern Arizona Veterans Administration registry showed a seizure IR of 3, 5, and 32 for mild, moderate, and severe TBI, respectively. The more severe the injury, the more likely the patient was to have post-traumatic seizures.

**Etiology of Seizures Following Injury**

Two main types of injury are related to seizure occurrence: direct trauma, which causes contusions, hemorrhage, and lacinations; and diffuse axonal injury (DAI), which involves the deep white matter. In the above studies, seizures were more common among patients with penetrating injuries or skull fractures, which may have been due to the direct irritation of the cortical gray matter, where seizures usually originate.

Certain EEG findings seen early after TBI may not be associated with epilepsy. In animal models, immediate EEG changes include high-amplitude spikes and sharp waves, followed by suppression of background impulses. However, these changes do not necessarily correlate with seizure activity. In human studies, little evidence of EEG changes after TBI has been noted. One study of boxers reported evidence of reduced EEG amplitude and irregular theta activity within about 15–30 minutes of a fight. In another study of patients who had sustained a TBI, generalized slowing was found in 43%, and focal slowing was noted in 32%. These patterns resolved after an average of 3 months. Generalized slowing takes longer to resolve than does focal slowing, which indicates the presence of a structural lesion; it commonly is seen among individuals with penetrating injuries and also may result from secondary diffuse axonal injury.

After trauma, the most common type of seizure seen is complex partial seizures. These occurrences commonly are preceded by an aura and have a wide variety of presentations, which depend on the origin of the seizure. However, several other disorders associated with episodic symptoms can mimic complex partial seizures. Affected patients often suffer stress and psychological damage from the injury, and they may experience dissociative events. In addition, they may have post-traumatic stress disorder (PTSD) along with paroxysmal nightmares, flashbacks, and panic attacks which could be mistaken for seizure activity. In addition, PTSD or acute stress may result in development of a conversion disorder or nonepileptic seizures/spells.

Thus, the risk of epilepsy or post-traumatic seizures is higher following severe head injuries than after mild TBI or concussions. The likelihood that seizures will also occur depends upon the type of injury sustained. Complex partial seizures occur most commonly following significant TBI; this phenomenon has diverse presentations. Finally, many conditions can mimic post-traumatic seizures.

**REFERENCES**


