COGNITIVE AND PSYCHIATRIC ISSUES ASSOCIATED WITH SEIZURE DISORDERS

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Presented as part of AAN course entitled:
The Burden of Epilepsy: Managing Comorbidities and Quality of Life
Date: Tuesday, April 25, 2017
Location: Boston, MA

Cognitive Issues of Epilepsy

Cognition may be affected by multiple factors in patients with epilepsy including: 1) etiology of the seizures; 2) seizure type and frequency; 3) age of epilepsy onset; 4) duration and severity of seizures; 5) structural cerebral lesions responsible for the development of epilepsy; 6) cerebral damage secondary to prolonged seizures; 7) disturbance of cerebral function in the interictal, ictal, or postictal states; 8) sequela of epilepsy surgery; 9) side effects of antiepileptic drugs (AEDs); and 10) psychosocial factors.[1]

Cognitive impairment may predate epilepsy and is present early in the course of epilepsy for many patients. Obviously, some conditions which impair cognition increase the risk of epilepsy (e.g., stroke, brain tumor, head trauma). In the first VA Co-op Study, patients with newly diagnosed, untreated epilepsy exhibited significant deficits compared to a healthy control population.[2] In a study of children with recent-onset idiopathic epilepsy, mild diffuse neuropsychological impairment and academic difficulties were present at the time of diagnosis.[3] A recent study also found high frequency of cognitive deficits in adults with newly diagnosed epilepsy before treatment.[4] A typical clinical approach to assessing cognitive deficits is to ask patients if they experiencing problems. However, there is a disparity of subjective and objective cognitive effects. The patient's subjective perception of cognitive performance is more related to their mood than their objective cognitive performance.[5]

In the 19th century before the advent of the first AEDs, epilepsy was viewed as a degenerative cerebral disease because repeated numerous convulsions clearly can impact cerebral function. In the setting of less severe seizures, the impact is less obvious, but can occur. In a study of patients with temporal lobe epilepsy, repeat MRIs revealed progressive hippocampal atrophy in patients with continued seizures.[6] In addition, patients with longer duration of epilepsy is associated with worse cognition, especially worsened seizure frequency and severity.[7,8]

AEDs reduce neuronal irritability to control seizures, but can reduce neuronal excitability and adversely affect cognitive function. The most common cognitive effects of AEDs include adverse effects on attention, vigilance, psychomotor speed, memory, and dual processing. The risks of cognitive side effects can be affected by AED titration rate, final dose, blood levels, specific AED used, polytherapy, and individual susceptibility. AEDs exhibit differential cognitive effects. Gabapentin, lacosamide, lamotrigine, and levetiracetam affect cognition the least. Barbiturates, benzodiazepines, phenobarbital, topiramate, and zonisamide are most likely to adversely affect cognition. Intermediate risks are seen with carbamazepine, oxcarbazepine, phenytoin, and valproate.[1,9] The cognitive effects of AEDs at the age extremes have been less studied. AED side effects and toxicity can negatively impact quality of life in patients with epilepsy.[10-11] Identifying AED adverse effects and altering AED regimens to reduce such effects can have a substantial impact on quality of life.

Particular concern has been raised over the effects of fetal AED exposures. The NEAD study was a large prospective investigation which enrolled 309 mother-child pairs during pregnancy and examined long-term cognitive outcome in children. At ages 3 and 6 years old, children exposed to valproate had reduced IQ and other cognitive abilities compared to children exposed to carbamazepine, lamotrigine, and phenytoin; these effects were dose dependent.[12-14] The NEAD Study also assessed the effects of breastfeeding when on AED. If women who were on AED during pregnancy, then breastfeed while taking AED, there is no adverse effects of the breastfeeding on cognition at age 3 years, and by age 6 years, the children who breastfed actually have higher IQ.[15-16]

Temporal lobe epilepsy surgery may pose cognitive risks including declines memory function, naming, and facial recognition. Predictors of this risk include: (1) language dominant anterior temporal lobectomy, (2) seizure onset at older age, (3) epilepsy surgery at older age, (4) higher preoperative cognitive performance, (5) lack of structural lesions (e.g., hippocampal atrophy or sclerosis), and (6) poor post-operative seizure control.[17] In contrast, preliminary results of laser amygdalo-hippocamptectomy appears to have less risk.[18] In addition, neurostimulation therapies for epilepsy do not entail cognitive risks, including vagal nerve stimulation (VNS), responsive neurostimulation (RNS), and deep brain stimulation (DBS).[19-21]

Psychiatric Issues in Epilepsy

Depression. Depression is underdiagnosed and undertreated in epilepsy patients. Depression is common in patients with epilepsy occurring in 30-50% of patients with medically-refractory epilepsy during their lifetime vs. approximately 10% in patients with controlled seizures.[22-24] Depression and epilepsy have a bi-directional relationship; epilepsy patients are not only more likely to develop depression, but people with depression are more likely to develop epilepsy.[25] Post-ictal depression occurs in about 50% of patients with medically refractory epilepsy, occurring within up to 5 days of a seizure.[25] Interictal Dysphoric Disorder (IDD) has features overlapping with Major Depressive Disorder (MDD), but IDD has a rapidly fluctuating course. In addition to depressed mood, fatigue, and changes in sleep pattern seen in MDD, it is more likely to also have prominent irritability, anhedonia, hopelessness, helplessness, fear, labile mood, and anxiety.[26] Suicide is increased up to 25 fold in epilepsy patients with suicide and suicide attempts occurring in 5-14% of epilepsy patients.[27-28] In addition, physicians should be aware that that most AEDs can produce negative behavioral effects.[1,9] However, some AEDs have positive psychotrophic effects and are used in a variety of psychiatric disorders (e.g., carbamazepine, lamotrigine, and valproate are used in bipolar disorder). The FDA issued a class label warning in January 2008 for all AEDs for an increased risk of suicidal ideation/behaviors. However, the FDA warning was based on a meta-analysis, and several problems have been raised with the FDA's: 1) data were not collected in a systematic and prospective manner; 2) all AEDs were lumped together despite three AEDs (i.e., carbamazepine, valproate, felbamate) showed no increased risk; and 3) risk of suicidality was greater in epilepsy patients than those with psychiatric disorders.[29] Thus, the role of AEDs as an independent factor in promoting suicide remains in doubt. Prompt diagnosis and successful treatment of psychiatric co-morbidities is important to maximize the quality of life of patients with epilepsy; however, depression is underdiagnosed and undertreated in epilepsy patients. Routine screening for depression and other psychiatric disorders should be done at least once per year.[30]

When considering treatment of depression in epilepsy, one should first consider whether AEDs which the patient is currently receiving AEDs that have negative psychotropic properties (benzodiazepines, felbamate, levetiracetam, phenobarbital, primidone, tiagabine, topiramate, vigabatrin, zonisamide).[1,9] Removal of these AEDs or addition of AEDs with positive psychotropic properties (carbamazepine, lamotrigine, valproate) might be helpful. Serotonin selective reuptake inhibitors (SSRIs) or cognitive behavioral therapy should be considered first line treatments for MDD in patients with epilepsy.

Anxiety. Disorders of anxiety are common in patients with medically-refractory partial epilepsy, occurring in about 19%.[31] Post-ictal symptoms occurring 6-24 hours after a seizure can include anxiety, panic, agoraphobia, compulsions, and self-consciousness.[32-33] The presence of comorbid anxiety and mood disorders increases the frequency of reported AED-related adverse events.[34]

Psychosis. Approximately 7% of patients with medically-refractory partial epilepsy develop psychosis.[35] Psychosis may be interictal or post-ictal (typically 48-72 hours after a seizure cluster). AEDs can rarely induce (e.g., levetiracetam, topiramate, zonisamide, or withdrawal from benzodiazepine). Interictal psychosis may require neuroleptic therapy, and post-ictal psychosis may respond to a short course of low dose benzodiazepines or neuroleptics, such as quetiapine or risperidone.

Conclusions: Physicians who treat patients with epilepsy should be aware of the major impact that cognitive impairment and psychiatric co-morbidities have on patients with epilepsy. Identifying and treating these co-morbidities in epilepsy patients is just as important as seizure treatment.

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