Epilepsy Concerns in Older Patients

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Epidemiology and Etiology

Among those with epilepsy, those over age 65 represent the fastest growing age-related subgroup. The incidence of epilepsy grows noticeably with advancing age, and reaches 85.9/100,000 for 65-69 year-olds and increases to greater than 150/100,000 in those greater than 80 years.[1] Nearly 10.5% of elderly nursing home residents receive anticonvulsants.[2]

In elderly patients with epilepsy, cerebrovascular etiologies account for up to one half of cases. Other etiologies for epilepsy in this age group include dementia (primarily Alzheimer's disease), brain tumors, and head trauma. Another large subgroup is cryptogenic, and vascular mechanisms are postulated to contribute significantly to this group as well.[3] Epilepsy risk is increased greater than 20 fold within one year after stroke. Cortical strokes, hemorrhagic strokes, and those with acute symptomatic seizures are more likely to lead to later epilepsy. Alzheimer's disease patients may have up to a ten-fold increased risk of epilepsy than those without this diagnosis.[4] A recent VA study found that stroke and dementia were the most common risk factors for the development of new-onset epilepsy—the combination of both was synergistic. Statin use carried a lower risk of epilepsy, as did hyperlipidemia, and obesity.[5] A case-control study in Quebec found a significantly reduced adjusted rate ratio of epilepsy among statin users than non-users[6] in those who underwent coronary revascularization, as well as a dose effect of statins on epilepsy expression. These statin study results are intriguing and await further biological explanation and replication.

Diagnostic Issues

The elderly do not always exhibit classical semiologies or auras as in the young. Semiologic analyses of seizures have revealed that subtle and brief periods of confusion are seen much more often in the elderly compared to younger adults. Almost 30% of older patients later diagnosed with epilepsy were first misdiagnosed with blackouts, syncope, altered mental status and confusion.[4] Postictal periods can be much more prolonged in this age group, lasting days.

The diagnosis of seizure in the elderly is made difficult by frequently limited or vague histories and by numerous competing diagnoses in this age group, including syncope and **transient ischemia attacks (TIA)**. Cognitive impairment in the patient may further confound the history. The events are often unwitnessed and confusional symptoms are common. Specialists may not be utilized as often to sift through these presentations. Falls may be ascribed to imbalance, particularly if a lapse in consciousness is underappreciated.

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Differential Diagnosis and Work-up

The differential diagnosis for spells in this group includes TIA, syncope (especially convulsive syncope), migraine with confusion, drug intoxication, infections, psychiatric disorders, transient global amnesia and dementia with superimposed delirium. Multiple metabolic etiologies should be sought. These include hypo- and hyperglycemia, thyroid dysfunction, hypercapnia, uremia and hyponatremia.

Electroencephalography (EEG) can be valuable, but beware potentially confounding false positive findings. A modest amount of temporal theta activity may be seen in drowsiness as a normal finding in this age group. Cerebrovascular disease may be associated with focal slowing. **Subclinical rhythmic electrographic discharges in adults (SREDA)** and wicket spikes represent two benign variant patterns that can mimic epileptiform phenomena. **Long-term video-EEG monitoring (LTM)** may be helpful in the work-up for those with recurrent spells that suggest seizure. Brain imaging (preferably MRI) is advised. As with EEG, numerous abnormalities may be found of uncertain significance in this age group and correlation with the clinical presentation and the EEG are needed. Other investigations to consider include electrocardiogram, holter monitoring, echocardiogram, tilt-table or sleep studies and/or vestibular testing, as appropriate, to explore other mimics.

Prolonged confusional states can be encountered, either as post-ictal phenomena, or as a manifestation of non-convulsive status epilepticus. This latter diagnosis requires a level of suspicion in elderly patients with unexplained stupor; EEG is necessary to make this diagnosis.

Management

In some older patients, especially those with cognitive impairment, help from caregivers with medications may be critical. A home safety evaluation may be helpful. Pro-convulsive medications in the patient's medication list should be re-evaluated and minimized, if possible.

Medical management of epilepsy in the elderly poses several distinct challenges. Aging leads to alterations in pharmacokinetic and pharmacodynamic parameters, increasing the risk for side effects of **anti-epileptic drugs (AEDs)** and decreasing the predictability of dose and blood level relationships. Protein binding may be occasionally lower in the aged, especially in those with poor nutritional status or other causes of hypoalbuminemia. Highly protein bound medications such as phenytoin and valproate may have higher free fractions in the elderly, which can promote clinical toxicity at lower total doses than in the young. Some elderly may have delayed absorption due to slower gastric emptying, or delayed intestinal transit time, as well as a lower overall volume of distribution. Decreased hepatic or particularly renal clearance in the older patient population can lead to unexpectedly higher serum AED levels.

The elderly tend to have more medical diagnoses and take more medications than a younger population, and thus, are at an intrinsically greater risk of drug-drug interactions.[2] A recent study found that 45.5% of VA patients had clinically meaningful potential drug-drug interactions with prescribed AEDs. Nearly half of these had multiple drug-drug interactions, and the most common related to cardiovascular medications.[7] Newer AEDs, as a group, exhibit fewer hepatic affects, are more often renally cleared, have lower protein binding, and thus have fewer drug interactions.

Numerous medications more common in the elderly pose significant reciprocal interactions with some AEDs. Highly protein bound AEDs (e.g. phenytoin and valproate) interact with other highly protein bound concomitant medications (e.g. warfarin), leading to complex untoward interactions affecting both the AED free levels and the degree of anticoagulation. Cytochrome P450-inducing AEDs (phenytoin, carbamazepine, phenobarbital) accelerate the clearance of many drugs that rely upon hepatic catabolism, including some antiarhythmics and antihypertensives, many cholesterol-lowering statins, and some psychotropics. Valproate is an example of an enzyme inhibitor, as are cimetidine, erythromycin, verapamil, among others. These enzyme inhibitors may increase circulating levels of some AEDs, potentially leading to AED toxicity.

Other co-morbidities are particularly germane to the older population with epilepsy. The older generation of AEDs particularly hasten bone demineralization. The elderly are at a higher risk of osteoporosis and balance issues, leading to falls and potentially to fractures. Cognitive concerns are enriched in the elderly as well. Some AEDs pose particular concerns to cognition (e.g. phenobarbital, topiramate) and may be less well tolerated in this population as a result. Hyponatremia, occasionally provoked by carbamazepine and more often with oxcarbazepine use, is more frequently encountered in the aged, particularly with concomitant diuretic use.

Treatment Choice

There have been three randomized, double-blind clinical trials for older patients with epilepsy. Most trials of AEDs have been conducted in younger adults. One UK study compared lamotrigine vs. immediate release carbamazepine in elderly with new-onset epilepsy. They found similar efficacy in both, but better tolerability in the lamotrigine arm.[3] A later international study compared lamotrigine with slow release carbamazepine and did not observe as marked a tolerability difference.[8] A VA study compared gabapentin vs. lamotrigine vs. immediate release carbamazepine in the elderly and found better tolerability in the gabapentin and lamotrigine arms vs. carbamazepine without efficacy advantages.[9] Open label studies with a variety of newer AEDs (e.g. oxcarbazepine, levetiracetam, and topiramate) in the elderly have demonstrated their potential value in this age group.[4] A VA study observed that patients taking phenobarbital, valproate, and gabapentin were less adherent to their AED regimen whereas those taking lamotrigine and levetiracetam were significantly more adherent.[10]

In treating the elderly, it is advised to keep the regimen as simple as possible. Seizure type may influence AED selection, but most elderly patients (particularly new-onset patients) will have partial onset seizures. Tolerability concerns should impact AED selection and choices individualized. Doses should begin quite low and titration should be slow, where possible. Cost concerns may be influential. The majority of elderly do respond to AED treatment. But, refractory epilepsy may occur in this group as in younger cohorts. Surgical resection is not as commonly used in this age group, though may be an option for a subset. Vagal nerve stimulation is another option for some when AEDs prove inadequate and surgery is not a viable option.

Summary

Epilepsy incidence is higher in the elderly than in younger adults. Diagnosis and management of the elderly with epilepsy presents several specific demands. A variety of other mimics can confound the diagnosis in this age group. Treatment choices should consider issues of metabolism, co-morbidities, and side effect profiles. Drug-drug interactions are prevalent and need to be minimized and/or anticipated.

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Discussion of off-label usage: gabapentin, levetiracetam, and topiramate.

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